Submission of Clinical Data Supporting Formulary Consideration of Lovaza™ (omega-3-acid ethyl esters) Capsules

Content for Online Formulary Kit

TABLE OF CONTENTS

Common abbreviations:

ALT	**=**	**alanine aminotransferase**
Apo	**=**	**apoliprotein**
AST	**=**	**aspartate aminotransferase**
BL	**=**	**baseline**
BMI	**=**	**body mass index**
CE	**=**	**cholesterol esters**
CETA	**=**	**cholesterol ester transfer activity**
CETP	**=**	**cholesterol ester transfer protein**
CV	**=**	**cardiovascular**
CVD	**=**	**cardiovascular disease**
CHD	**=**	**coronary heart disease**
DHA	**=**	**docosahexaenoic acid**
EPA	**=**	**eicosapentaenoic acid**
FCHL	**=**	**familial combined hyperlipidemia**
GI	**=**	**gastrointestinal**
HDL-C	**=**	**high-density lipoprotein cholesterol**
hs CRP	**=**	**high-sensitivity C-reactive protein**
HTG	**=**	**hypertriglyceridemia**
LDL-C	**=**	**low-density lipoprotein cholesterol**
Lp (a)	**=**	**lipoprotein (a)**
Lp-PLA2	**=**	**lipoprotein-associated phospholipase 2**
mg/d	**=**	**milligram per day**
mg/dL	**=**	**milligram per deciliter**
MI	**=**	**myocardial infarction**
mmol	**=**	**millimole**
NCEP	**=**	**National Cholesterol Education Program**
NL	**=**	**neutral lipid**
nm	**=**	**nanometer**
PLTA	**=**	**phospholipid transfer activity**
PUFA	**=**	**polyunsaturated fatty acids**
SD	**=**	**standard deviation**
sdLDL	**=**	**small dense low-density lipoprotein**
SEM	**=**	**standard error of the mean**
TC	**=**	**total cholesterol**
TG	**=**	**triglyceride**
ULN	**=**	**upper limits of normal**
VLDL	**=**	**very low-density lipoproteins**

1.0 Product information

1.1 AHFS Classification

24:06 Antilipemic Agents

24.06.92: Antilipemic Agents, Miscellaneous

1.2 Product Description

Lovaza™, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Lovaza™ (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA—approximately 465 mg) and docosahexaenoic acid (DHA—approximately 375 mg).[1]

The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight is 330.51. The structural formula of EPA ethyl ester is shown in Figure 1.1[1]

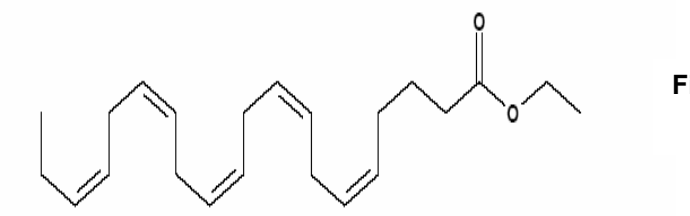


Figure 1.1 Structural Formula of EPA Ethyl Ester

The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight is 356.55. The structural formula of DHA ethyl ester is shown in Figure 1.2[1]

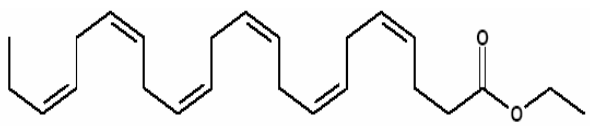


Figure 1.2 Structural Formula of DHA Ethyl Ester

Lovaza™ capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).[1]

1.3 DOSAGE FORMS SUPPLIED

Table 1.1 Dosage Forms of Lovaza™[1]

Dosage Form	Strength	Color	Package Size	NDC #	AWP ($)	WAC ($)
Capsule	1 g	Transparent soft-gelatin capsule filled with light-yellow oil	60	65726-425-15	$74.88	$62.40
Capsule	1 g	Transparent soft-gelatin capsule filled with light-yellow oil	120	65726-0425-27	$149.76	$124.80

1.4 Indications

1.4.1 FDA-Approved Indications

Very high triglycerides: monotherapy
Lovaza™ is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥ 500 mg/dL) TG levels.[1]

Usage Considerations
In individuals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important contributing factors and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta-blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent, if medically indicated, may obviate the need for specific drug therapy for hypertriglyceridemia.[1]

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.[1]

1.4.2 Non–FDA-Approved Uses

Off-label uses of omega-3-acid ethyl esters include:

- **Treatment of IgA Nephropathy**

  IgA nephropathy, the most common primary glomerulonephritis, is a chronic kidney disease that may progress over a period of from 10 to 20 years, and can lead to end-stage renal disease.[3] It is caused by deposition of immunoglobulin A within the glomeruli of the kidneys, which prevents the filtering process of blood. In vitro and animal studies have shown that

treatment with omega-3 polyunsaturated fatty acids (PUFA) decrease histologic evidence of glomerular damage.[4]

Donadio and associates compared the effects of Lovaza™ 8 g/d versus Lovaza™ 4 g/d administered over 2 years to patients with severe IgA nephropathy.[5] Both doses showed similar rates of renal function loss (within-patient annualized slope for serum creatinine). Survival free of end-stage renal disease (75% at 3 years) was also similar in the 2 Lovaza™ groups. Lovaza™ was well tolerated, and there were no unfavorable effects on lipids, hematocrit, peripheral blood leukocytes, or platelets. Because treatment with high-dose Lovaza™ conferred no added benefit, investigators concluded that 4 g/ d was an appropriate dose for high-risk patients with IgA nephropathy, including those with moderately advanced renal disease.

The efficacy of omega-3 PUFA has been tested in patients with IgA nephropathy in 4 randomized trials. One study showed that treatment stabilized renal function, as indicated by a lack of change in the reciprocal of serum creatinine.[5, 6] Two smaller studies reported a decline in renal function.[7, 8] A meta-analysis of these studies plus a small nonrandomized study estimated that the probability of beneficial effect of omega-3 PUFA on the preservation of renal function was 75%.[9]

- **Secondary Prevention Post Myocardial Infarction**

The GISSI-Prevenzione study was a 3.5-year randomized, multi-center European prospective study of the independent and combined effects of Lovaza™ 1 g/d and vitamin E on morbidity and mortality among more than 11,000 patients surviving recent (<3 months) myocardial infarction (MI).[10] Findings, which yielded more than 38,000 patient-years of data during an average 3.5-year follow-up demonstrated that there was a 10% to 15% relative decrease in the combined primary endpoint of death, nonfatal MI, and nonfatal stroke with Lovaza™ when compared with control (no treatment). In addition, Lovaza™ 1 g/d was associated with a 45% reduction in the risk of sudden death; a 20% relative decrease in all fatal events and a 30% decrease in cardiovascular (CV) deaths. The rate of nonfatal CV events was unchanged.

A post-hoc analysis of the data examined the time course of mortality benefits associated to treatment with Lovaza™.[11] There was a significant early treatment effect for total survival (all fatal events) after 3 months of treatment with Lovaza™ (41% risk reduction, *P* =.037) that persisted throughout the study. At 4 months, the risk of sudden death was reduced by 53% (*P* =.048) and by the end of the study risk of sudden death was 44% (*P* =.0006).

Lovaza™ is currently distributed in more than 40 countries around the world including France, Germany, Italy, Japan, Spain, and the United Kingdom. In all of these countries, Lovaza™ (known as Omacor) is approved for secondary prevention after MI and for treatment of HTG as mono- or combined therapy with statins. Doses are generally 1 g/d for secondary prevention, and 2 to 4 g/d for treatment of HTG.

- **Prevention of Atrial Fibrillation Post Coronary Artery Bypass Surgery**

Calo and associates studied the effects of Lovaza™ 2 g/d in the prevention of atrial fibrillation after coronary artery bypass surgery (CABG) in 160 patients.[12] Patients who received Lovaza™ experienced significantly fewer occurrences of atrial fibrillation than those patients in the control group who received usual care (15.2% vs 33.3%; *P* =.013). In addition, after CABG, patients in the Lovaza™ group had a shorter length of hospital stay than those in the control group (7.3 ± 2.1 days vs 8.2 ± 2.6 days, *P* =.017). Lovaza™ was well tolerated; there were no significant differences between groups in the incidence of nonfatal postoperative complications or postoperative mortality (*P* =.8 and *P* = 1.0, respectively).

- **Effects on Inflammation**

  Many anti-inflammatory pharmacotherapies are directed at inhibiting the production of inflammatory mediators, which include the omega-6 eicosanoids, prostaglandin E2 (PGE2), and leukotriene B4 (LTB4) as well as the cytokines, interleukin 1b (IL-1b), and tumor necrosis factor α (TNF-α).[13] EPA, an omega-3 fatty acid, competes with arachidonic acid (AA), an omega-6 fatty acid, for prostaglandin and leukotriene synthesis at the cyclooxygenase and lipoxygenase level. Studies have shown that when consumption of omega-3 fatty acids increases, the production of the more harmful inflammatory mediators such as PGE2 and LTB4 decreases, which leads to suppression of cytokine synthesis.[14]

  Given that cytokines such as IL-1, TNF-α, and IL-6 have been detected in high amounts in patients with rheumatoid arthritis, Sundrarjun and colleagues assessed the effects of Lovaza™ on serum pro-inflammatory cytokine concentrations and clinical variables in patients with active rheumatoid arthritis.[15] Sixty patients were randomized to receive either Lovaza™ 4 g/d, placebo, or no intervention (control group). Enrolled patients were followed for 24 weeks, encompassing a 6-week dietary advice period, a 12-week treatment period, and a 6-week follow-up period. After 24 weeks, treatment with Lovaza™ resulted in a significant reduction in serum CRP levels from baseline (-11.1%; $P < .05$); a correlation between the levels of IL-6 and CRP ($r = 0.62$, $P < .05$) was observed. There were no significant differences in these variables among the 3 groups at 24 weeks. No significant reductions in swollen or tender joint counts were observed in either the Lovaza™ or placebo groups.

  Omega-3 fatty acids may also decrease inflammation in atherosclerotic plaques. Cawood and associates determined that omega-3 fatty acids reduce inflammation in atherosclerotic plaques that are in advanced stages. In a randomized clinical trial, 121 patients awaiting carotid endarterectomy received either Lovaza™ 2 g/d or olive oil (placebo) until surgery (7 to 109 days; median 22 days). The fatty acid composition of plaque phospholipids, mRNA levels of matrix metalloproteinases (MMPs, which degrade atherosclerotic plaques leading to instability and rupture) and intercellular adhesion molecule (ICAM 1) were measured. Patients in the Lovaza™ group had higher EPA content in plaque phospholipids ($P < .0001$) and expressed lower levels of mRNA for MMP7, MMP9, MMP12, and ICAM-1 ($P < .05$).[16]

1.4.3 Use of Lovaza™ in the Treatment of Hypertriglyceridemia: New Data

Reduction of Non–HDL-C Levels: a Secondary Target of Lipid Therapy

Non–HDL-C levels are highly correlated with ApoB, the major apolipoprotein of all atherogenic lipoproteins. In most patients with TG levels <200 mg/dL, VLDL-C levels are not substantially elevated, thus non–HDL-C correlates highly with LDL-C. Typically, VLDL-C levels are ≤30 mg/dL when TG levels are <150 mg/dL. However, when TG levels are ≥200 mg/dL, VLDL-C levels are distinctly raised. Thus, a reasonable goal for non–HDL-C is one that is 30 mg/dL higher than the LDL-C goal. As a secondary target of therapy, non–HDL-C allows more flexibility in choice of therapies to reduce atherogenic lipoproteins contained in the combined LDL+VLDL fraction.[17] Davidson and associates compared the effects of Lovaza™ 4 g/d as an add-on treatment to patients with persistent hypertriglyceridemia (baseline TG levels between 200-400 mg/dL), while on stable simvastatin (40 mg/day) therapy. The addition of Lovaza™ to simvastatin therapy resulted in a significant reduction in non–HDL-C levels compared with the placebo group (-9% vs -2%).

Effects on Lipoprotein Particle Size, Particle Concentration and Subfractions in Patients with Persistent Hypertriglyceridemia

Increase in LDL particle size in patients with persistent hypertriglyceridemia:

A sub-analysis of the OM-6 COMBOS study assessed the influence of TG-lowering with Lovaza™ on LDL particle size in patients with TG levels between 200 and 499 mg/dL while on stable statin therapy. Median LDL particle size increased in the Lovaza™ group (19.90 nm to 20.20 nm, *P* = .007 vs. placebo). Median changes from baseline were 0.60, 0.40, 0.15, and -0.20 nm, when the on-treatment TG concentrations were <150, 150-199, 200-249 and ≥250 mg/dL, respectively (P < 0.001). The association of on-treatment TG category with the change in LDL particle size remained highly significant (*P* < .001) after adjusting for the degree of TG-lowering.[18]

Changes in lipoprotein particle concentrations in response to a decrease in Lp-PLA2 levels:

A sub-analysis of the OM-6 COMBOS study assessed the influence of TG-lowering with Lovaza™ on Lp-PLA2 concentration and lipoprotein subfraction levels in patients with TG levels between 200 and 499 mg/dL while on statin therapy. Treatment with Lovaza™ lowered Lp-PLA2 concentration (231 ng/mL to 200 ng/mL, P = .002 vs placebo). Thus, Lovaza™-induced changes in Lp-PLA2 response were associated with changes in LDL and HDL particle concentrations, and differentially related to changes in subfractions of these lipoproteins.[19]

Changes in lipoprotein levels and particle concentrations in response to a decrease in ApoC-III levels:

A sub-analysis of the OM-6 COMBOS evaluated the effect of Lovaza™ on ApoC-III and lipoprotein subfraction levels in patients with TG levels between 200 and 499 mg/dL while on stable statin therapy. In the Lovaza™+ simvastatin group, ApoC-III was significantly reduced compared with placebo (−7.1% vs + 3.8%, *P* < .001). Reductions in ApoC-III were significantly correlated (all *P* < .01) with reductions in VLDL-C (r = 0.56), TGs (r = 0.51), remnant lipoprotein particle cholesterol (r = 0.43), and LDL-C (r = 0.27), and inversely correlated with an increase in LDL particle size (r = –0.23). In addition, lowering of ApoC-III was associated with a reduction in small LDL particles (r = 0.32) and an increase in large HDL particles (r = –0.24).These results are consistent with the hypothesis that reductions in ApoC-III may contribute to enhanced conversion of VLDL to LDL, as well as to increased lipolysis and reduced circulatory residence for TG-rich lipoproteins.[20]

1.5 Clinical Pharmacology

1.5.1. Mechanism of Action in Hyperlipidemia

The mechanism of action of Lovaza™ is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Lovaza™ may reduce the synthesis of TGs in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.[1]

1.5.2 Pharmacokinetic and Bioavailability Studies

In healthy volunteers and in patients with hypertriglyceridemia, EPA, and DHA were absorbed when

administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Lovaza™) induced significant, dose-dependent increases in the EPA content of serum phospholipids; increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Lovaza™ was independent of age (<49 years vs ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Lovaza™ in children are not available.[1]

1.6 Clinical Studies

1.6.1 High Triglycerides: Add-on to HMG-CoA Reductase Inhibitor Therapy

The effects of Lovaza™ 4 g/d as add-on to treatment with simvastatin were evaluated in a randomized, double-blind, placebo-controlled, parallel-group study of 254 adult patients (122 on Lovaza™ and 132 on placebo) with persistent high triglycerides (200-499 mg/dL) despite simvastatin therapy (Table 2). Patients were treated with open-label simvastatin 40 mg/d for 8 weeks prior to randomization to control their LDL-C levels to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. The addition of Lovaza™ (4 g/d) to simvastatin therapy for 8 weeks resulted in a significant decrease in non–HDL-C levels (primary endpoint) compared with the placebo group.[1]

The changes in the major lipid and lipoprotein parameters for the Lovaza™ plus simvastatin and the placebo plus simvastatin groups are given in Table 1.2.

Table 1.2 Response to the Addition of Lovaza™ 4 g/d to Ongoing Simvastatin 40 mg/d Therapy in Patients with High Triglycerides (200-499 mg/dL)[1]

Parameter	Lovaza™ + Simvastatin N=122			Placebo + Simvastatin N=132			Difference	P-value
	BL	EOT	Median % Change	BL	EOT	Median % Change		
Non–HDL-C	137.0	122.8	-9.0	141.3	133.5	-2.2	-6.8	<.0001
TG	267.8	182.3	-29.5	270.7	259.5	-6.3	-23.2	<.0001
TC	184.3	172.0	-4.8	183.5	178.0	-1.7	-3.1	.0013
VLDL-C	51.5	36.5	-27.5	52.0	48.5	-7.2	-20.3	<.0001
Apo B	85.5	80.0	-4.2	86.8	84.5	-1.9	-2.3	.0232
HDL-C	46.0	48.0	+3.4	43.3	44.0	-1.2	+4.6	<.0001
LDL-C	90.7	87.5	+0.7	85.0	85.0	-2.8	+3.5	.0522

BL=Baseline (mg/dL); EOT=End of Treatment (mg/dL); Median % Change=Median Percent Change from Baseline; Difference=Lovaza™ Median % Change – Placebo Median % Change; Non–HDL-C=Non–high-density Lipoprotein Cholesterol; TG=Triglycerides; TC=Total Cholesterol; VLDL-C=Very Low-density Lipoprotein Cholesterol; Apo B=Apoprotein B; HDL-C=High-density Lipoprotein Cholesterol; LDL-C=Low-density Lipoprotein Cholesterol.

Lovaza™ 4 g/d significantly reduced non–HDL-C, TG, total cholesterol (TC), VLDL-C, and apoB levels and increased HDL-C and LDL-C from baseline relative to placebo.[1]

1.6.2 Very High Triglycerides: Monotherapy

The effects of Lovaza™ 4 g/d were assessed in 2 randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (Lovaza™ group n = 42, placebo group n = 42) with very high TG levels (Table 1.3). Patients whose baseline TG levels were between 500 and 2000 mg/dL were enrolled in these 2 studies of 6 and 16 weeks duration. The median TG and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.[1]

Table 1.3 Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥500 mg/dL) [1]

	TG		LDL-C		TC		HDL-C		VLDL-C		Non–HDL-C	
	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg
Placebo	788	+6.7	108	-4.8	314	-1.7	24	0.0	175	-0.9	292	-3.6
Lovaza™ 4g/d	816	-44.9	89	+44.5	296	-9.7	22	+9.1	175	-41.7	271	-13.8
Difference		**-51.6**		**+49.3**		**-8.0**		**+9.1**		**-40.8**		**-10.2**

BL = Baseline (mg/dL); % Chg = Median Percent Change from Baseline; Difference = Lovaza™ Median % Change – Placebo Median % Change

Lovaza™ 4 g/d reduced median TG, VLDL-C, and non–HDL-C levels and increased median HDL-C from baseline relative to placebo. Lovaza™ treatment to reduce very high TG levels may result in elevations in LDL-C and non–HDL-C in some individuals. Patients should be monitored to ensure that their LDL-C level does not increase excessively.[1]

The effect of Lovaza™ on the risk of pancreatitis in patients with very high TG levels has not been determined.[1]

The effect of Lovaza™ on CV mortality and morbidity in patients with elevated TG levels has not been determined.[1]

1.7 Contraindications

Lovaza™ is contraindicated in patients who exhibit hypersensitivity to any component of this medication.[1]

1.8 Precautions

General

Initial Therapy

Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Lovaza™ therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta-blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.[1]

Continued Therapy

Laboratory studies should be performed periodically to measure the patient's TG levels during Lovaza™ therapy. Lovaza™ therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.[1]

Information for Patients

Lovaza™ should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.[1]

Laboratory Tests

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza™ therapy. In some patients, Lovaza™ increased LDL-C levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza™ therapy.[1]

Anticoagulants

Omega-3 fatty acids have been shown to have antithrombotic effects and prolong bleeding time.[21] The prolongation of bleeding time that was reported was within normal limits and did not produce clinically significant bleeding episodes.[1] Further, to date no published studies have demonstrated significant changes in bleeding time or propensity for bleeding among patients treated with FDA-approved doses of Lovaza™.[22] A study of the interaction between fish oil and warfarin did not show increases in major bleeding episodes, or the need to reduce the dosage of warfarin did not arise.[23] Moreover, omega-3 fatty acid therapy in patients receiving aspirin or other antiplatelet agents has not been associated with an increase in bleeding.[22,24] A recent review of the literature on the risk of bleeding associated with omega-3 fatty acids concluded that the risk of clinically significant bleeding was virtually nonexistent.[22] Nevertheless, the FDA does mandate that patients should be given large doses of omega-3 fatty acids only under physician supervision. Although additional blood testing is not required for patients taking approved doses of Lovaza™, patients should be monitored for signs and symptoms of bleeding prior to, and throughout, treatment with Lovaza™.[1]

HMG-CoA Reductase Inhibitors

In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg/d with Lovaza™ 4 g/d did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin, at steady state.[1]

Cytochrome P450-Dependent Monooxygenase Activities

Omega-3-fatty acid containing products have shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Lovaza™ to induce P450 activities in humans has not been studied.[1]

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats omega-3-acid ethyl esters were administered by oral gavage at doses of 100, 600, or 2000 mg/kg body weight/day. Treatment of male rats for 101 weeks and females for 89 weeks did not result in increased incidence of tumors, up to 5 times human systemic exposures following an oral dose of 4 g/d based on a body surface area comparison. Standard lifetime carcinogenicity bioassays were not conducted in mice.[1]

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.[1]

In a fertility study, omega-3-acid ethyl esters were given at oral gavage doses of 100, 600, or 2000 mg/kg/d to male rats for 10 weeks prior to mating and to female rats for 2 weeks prior to and throughout mating, gestation, and lactation. Results showed no adverse effect on fertility at 2000 mg/kg/d.[1]

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Lovaza™ can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

Lovaza™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1]

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/d (28 g/d) based on a body surface area comparison.[1]

Female rats given oral gavage doses of 100, 600, or 2000 mg/kg/d of omega-3-acid ethyl esters for 2 weeks prior to mating and continued through gestation and lactation showed no adverse effects in the high-dose group (5 times human systemic exposure following an oral dose of 4 g/day, based on body surface area comparison).[1]
Pregnant rats given oral gavage doses of 1000, 3000, or 6000 mg/kg/day of omega-3-acid ethyl esters from gestation day 6 thorough 15 showed no adverse effects (14 times human systemic exposure following an oral dose of 4 g/d based on a body surface area comparison).[1]

Pregnant rats given oral gavage doses of 100, 600, or 2000 mg/kg/d from gestation day 14 through lactation day 21 showed no adverse effects in the high-dose group (5 times the human systemic exposure following an oral dose of 4 g/d based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/d (7 times the human systemic exposure following an oral dose of 4 g/d based on a body surface area comparison).[1]

In pregnant rabbits given oral gavage doses of 375, 750, or 1500 mg/kg/d from gestation day 7 through 19, no effects were observed in the fetuses in groups given 375 mg/kg/d (2 times human systemic exposure following an oral dose of 4 g/d based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/d based on a body surface area comparison).[1]

Nursing Mothers
It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovaza™ is administered to a woman who is breastfeeding.[1]

Pediatric Use
Safety and effectiveness in pediatric patients under 18 years of age have not been established.[1]

Geriatric Use
A limited number of patients over 65 years of age were enrolled in the clinical studies. In the pooled analyses, safety and efficacy findings in subjects over 60 years of age did not appear to differ from those of subjects less than 60 years of age.[1]

1.9 Adverse Reactions

Treatment-emergent adverse events reported in at least 1% of patients treated with Lovaza™ 4 g/d or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 1.4. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Lovaza™ and 2.6% of patients treated with placebo. Additional adverse events reported by 1 or more patients from 22 clinical studies for hypertriglyceridemia are listed below.[1]
BODY AS A WHOLE: enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, and sudden death.[1]

CARDIOVASCULAR SYSTEM: arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.[1]
DIGESTIVE SYSTEM: anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.[1]

Table 1.4 Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Hypertriglyceridemia That Used Lovaza™ 4 g/d[1]

BODY SYSTEM Adverse Event	Lovaza™ (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term. *Placebo was corn oil for all studies.

HEMATOLOGIC-LYMPHATIC SYSTEM: lymphadenopathy.[1]

INFECTIONS AND INFESTATIONS: Viral infection.[1]

METABOLIC AND NUTRITIONAL DISORDERS: edema, hyperglycemia, increased ALT, and increased AST.[1]

MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.[1]

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS):
Colonic polyp, renal cyst.[1]

NERVOUS SYSTEM: central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.[1]

RESPIRATORY SYSTEM: asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.[1]

SKIN: alopecia, eczema, pruritis, and sweating.[1]

SPECIAL SENSES: cataract.[1]

UROGENITAL SYSTEM: cervix disorder, endometrial carcinoma, epididymitis, and impotence.[1]

1.10 Drug Interactions

Cytochrome P450-Dependent Monooxygenase Activities

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 µM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 µM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Because the free forms of the EPA and DHA are undetectable in the circulation (<1 µM), clinically significant drug–drug interactions due to inhibition of P450-mediated metabolism EPA/DHA combinations are not expected in humans.[1]

1.11 Dosage and Administration

Patients should be placed on an appropriate lipid-lowering diet before receiving Lovaza™, and should continue this diet during treatment with Lovaza™. In clinical studies, Lovaza™ was administered with meals. The daily dose of Lovaza™ is 4 g/d. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).[1]

1.12 Drug Abuse and Dependence

Lovaza™ does not have any known drug abuse or withdrawal effects.[1]

1.13 Comparator Tables

(Note: all information obtained from Product Inserts)

Table 1.5 Descriptions: Chemical Class, Mechanism of Action

Brand	Chemical Class	Mechanism of Action
Lovaza™ (omega-3-acid ethyl esters), capsules	omega-3-acid ethyl ester	The mechanism of action of Lovaza™ is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Lovaza™ may reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.[1]
ANTARA® (fenofibrate capsules) micronized	fibric acid derivative	In animal models and hepatocyte cultures, fenofibrates were shown to activate peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting decrease in TG levels produces an alteration in the size and composition of LDL-C from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are
TRICOR® (fenofibrate tablets)		

		catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II, and HDL-C.[25, 26]
LOPID® (gemfibrozil tablets, USP)		Not definitely established. May inhibit peripheral lipolysis and decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. [93, Lopid PI, 2007, p. 4U] May also reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces. [27]
NIASPAN® (niacin extended-release tablets)	water-soluble, B complex vitamin	Not well defined. May include partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron TG removal from plasma. [28]

Table 1.6 Dosage Forms and Administration

Brand	Dosage Forms	Administration
Lovaza™ (omega-3-acid ethyl esters), capsules	1 g	Very high TG: daily dose is 4 g/ day.[1] May be taken as a single 4-g dose (4 capsules) or as two 2-g doses bid. In clinical studies, Lovaza™ was administered with meals.
ANTARA® (fenofibrate capsules) micronized	43, 87, 130 mg	Hypercholesterolemia or hyperlipidemia: initial dose is 130 mg/ day [26] Hypertriglyceridemia: initial dose is 43 to 130 mg per day[26] Can be taken without regard to meals.
TRICOR® (fenofibrate tablets)	54, 160 mg	Hypercholesterolemia or hyperlipidemia: initial dose is 160 mg per day[25] Hypertriglyceridemia: initial dose is 54 to 160 mg per day with food.[25]
LOPID® (gemfibrozil tablets, USP)	600 mg	600 mg BID taken 30 minutes before the morning and evening meal: daily dose of 1200 mg[27]
NIASPAN® (niacin extended-release tablets)	500, 750, 1000 mg	Initiate at 500 mg qhs for 4 wks to reduce incidence and severity of side effects. Increase to 1000 mg qhs for wks 5 to 8. Titrate to 1500 or 2000 mg qhs per patient clinical response and tolerance. Do not increase daily dose more than 500 mg in a 4-wk period; doses > 2000 mg are not recommended. Take at bedtime, after a low-fat snack.[28]

Table 1.7 FDA-Approved Indications

Brand	FDA-Approved Indications
Lovaza™ (omega-3-acid ethyl esters) capsules	As monotherapy in adult patients with[1]: -Very high TG levels (≥500 mg/dL) As an adjunct to diet, after reasonable attempts have been made to obtain satisfactory results with non-drug methods.
ANTARA® (fenofibrate capsules) micronized TRICOR® (fenofibrate tablets)	For adult patients with: [26,25] -Primary hypercholesterolemia -Mixed dyslipidemia (Fredrickson Types IIa and IIb) -Hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia As an adjunct to diet when response to diet and non-pharmacological interventions alone have been inadequate.
LOPID® (gemfibrozil tablets, USP)	For adult patients with:[27] -Hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia) who present a risk of pancreatitis. These patients typically have serum TG >2000 mg/dL, with elevated VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia). As an adjunct to diet when response to diet and non-pharmacological interventions alone have been inadequate. May be considered for TG levels between 1000 and 2000 mg/dL in patients with a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. -Indicated to reduce the risk of developing coronary heart disease (CHD) in Type IIb patients with no history or symptoms of CHD, who have had inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid,) and who have the following triad of lipid abnormalities: low HDL-C, high LDL-C and elevated TG levels. The potential benefit of gemfibrozil in treating type IIA patients with elevated LDL-C only is unlikely to outweigh the risks, due to potential toxicity such as malignancy, gallbladder disease, abdominal pain leading to appendectomy and other abdominal surgeries. An increased incidence in non-coronary mortality and a 44% relative increase in age-adjusted all-cause mortality were observed during the trial period with clofibrate, a chemically and pharmacologically related drug to gemfibrozil.
NIASPAN® (niacin extended-release tablets)	For adult patients with:[28] -Primary hypercholesterolemia -Mixed dyslipidemia (Fredrickson Types IIa and IIb) As an adjunct to diet when response to diet and non-pharmaco-logical interventions alone have been inadequate. -Also as indicated above, in combination with lovastatin in patients who require further TG lowering, LDL-C lowering, or HDL-C raising. -In combination with a bile acid binding resin, indicated adjunct to diet for adult with primary hypercholesterolemia (Type IIa) when response to diet or diet + monotherapy has been inadequate. -For adults with: hypertriglyceridemia (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who respond inadequately to a determined dietary effort. Such patients typically have serum TG levels over 2000 mg/dL, elevated VLDL-C, and fasting chylomicrons (Type V hyperlipidemia). May be considered for those patients with TG elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. -Indicated to reduce recurrent nonfatal MI risk in patients with history of MI and hypercholesterolemia. -In combination with a bile acid binding resin, niacin is indicated to slow progression, or promote regression, of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hypercholesterolemia.

Table 1.8 Pharmacokinetics

Brand	Pharmacokinetics
Lovaza™ (omega-3-acid ethyl esters) capsules	In healthy volunteers and in patients with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Lovaza™) induced significant, dose–dependent increases in EPA content of serum phospholipids, whereas increases in DHA content were less marked and not dose-dependent. Uptake of EPA and DHA into serum phospholipids in subjects treated with Lovaza™ was independent of age (<49 years vs. ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Lovaza™ in children are not available.[1]
ANTARA® (fenofibrate capsules) micronized	Plasma concentrations of fenofibric acid after multiple dose administration of Antara 130 mg capsules are equivalent, under low-fat fed conditions, to 200 mg fenofibrate capsules.[26]
TRICOR® (fenofibrate tablets)	Under fed conditions, plasma concentrations of fenofibric acid after administration of 54 mg and 160 mg tablets are equivalent to 60 mg and 200 mg capsules, respectively.[25]
LOPID® (gemfibrozil tablets, USP)	N/A
NIASPAN® (niacin extended-release tablets)	N/A

Table 1.9 Absorption

Brand	Absorption
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available.
ANTARA® (fenofibrate capsules) micronized	The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract.[26] Following oral administration in healthy volunteers, ~60% of a single dose of radio labeled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Doses of 2 or 3 capsules of 43 mg ANTARA (fenofibrate) given concurrently were dose-equivalent to single-capsule doses of 87 mg and 130 mg, respectively. The extent of absorption of fenofibric acid was unaffected when ANTARA® was taken either in fasted state or with a low fat meal. However, the C_{max} of ANTARA® increased in presence of a low-fat meal. T_{max} was unaffected in the presence of a low-fat meal. In the presence of a high fat meal, there was a 26% increase in AUC and 108% increase in C_{max} of fenofibric acid from ANTARA® relative to fasting state. Peak plasma levels of fenofibric acid from ANTARA® occur within 4 to 8 h after administration. There was less than dose-proportional increase in the systemic exposure of fenofibric acid from three strengths (43 mg, 87 mg, and 130 mg) of ANTARA® under fasting conditions.
TRICOR® (fenofibrate tablets)	The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. [25] Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 h after administration. The absorption of fenofibrate is increased when administered with food. With fenofibrate tablets, the extent of absorption is increased by ~35% under fed vs fasting conditions
LOPID® (gemfibrozil tablets, USP)	LOPID® is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in 1 to 2 hours, with a plasma half-life of 1.5 hours following multiple doses.[27] Gemfibrozil is completely absorbed after oral administration of LOPID® tablets. Gemfibrozil pharmacokinetics is affected by the timing of meals relative to time of dosing. In one study, both the rate and extent of

	absorption of drug were significantly increased when administered 0.5 hours before meals. Average AUC was reduced by 14% to 44% when LOPID® was administered after meals vs 0.5 hour before meals. In a subsequent study, rate of absorption of LOPID® was maximal when administered 0.5 hours before meals with the C_{max} 50% to 60% greater than when given either with meals or fasting. In this study, there were no significant effects on AUC of timing of dose relative to meals.
NIASPAN® (niacin extended-release tablets)	Niacin is rapidly and extensively absorbed (at least 60 to 76% of dose) when administered orally. To maximize bioavailability and reduce the risk of gastrointestinal upset, administration of NIASPAN® with a low-fat meal or snack is recommended. Single-dose bioavailability studies have demonstrated that NIASPAN® tablet strengths are not interchangeable.[28]

Table 1.10 Distributions

Brand	Distribution
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available.
ANTARA® (fenofibrate capsules) micronized	In healthy volunteers, steady-state plasma levels of fenofibric acid were shown within a week of dosing and did not demonstrate accumulation over time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. [26]
TRICOR® (fenofibrate tablets)	In healthy volunteers, steady-state plasma levels of fenofibric acid were shown within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. [25]
LOPID® (gemfibrozil tablets, USP	Not available.
NIASPAN® (niacin extended-release tablets)	Studies using radiolabelled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney, and adipose tissue. [28]

Table 1.11 Metabolism

Brand	Metabolism
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available.
ANTARA® (fenofibrate capsules) micronized	Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.[25, 26] Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine. *In vivo* metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.
TRICOR® (fenofibrate tablets)	
LOPID® (gemfibrozil tablets, USP)	LOPID® mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite.[27]
NIASPAN® (niacin extended-release tablets)	PK is complicated due to rapid, extensive first-pass metabolism, which is species- and dose-rate specific. [28] One pathway is a conjugation step with glycine to form nicotinuric acid (NUA). NUA is excreted in the urine, but there may be a small amount of reversible metabolism back to niacin. Another pathway forms nicotinamide adenine dinucleotide (NAD). Nicotinamide is further metabolized to N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is

	further metabolized to: N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). At doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between dose and plasma concentrations following multiple-dose administration. Nicotinamide does not have hypolipidemic activity. The activity of other metabolites is unknown. Mean Steady-State Pharmacokinetic Parameters for Plasma Niacin: — 1000 mg (2 × 500 mg) per day: C_{max}: 0.6 (µg/mL); T_{max}: 5 hrs — 1500 mg (2 × 750 mg) C_{max}: 4.9 (µg/mL); T_{max}: 4 hrs — 2000 mg (2 × 1000 mg) C_{max}: 15.5 (µg/mL); T_{max}: 5 hrs

Table 1.12 Excretion

Brand	Excretion
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available.
ANTARA® (fenofibrate capsules) micronized	After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. [26] After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces. Fenofibrate acid from ANTARA® is eliminated with a half-life of 23 hours, allowing once daily administration in a clinical setting.
TRICOR® (fenofibrate tablets)	After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. [25]After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces. Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.
LOPID® (gemfibrozil tablets, USP)	Approximately 70% of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. 6% of the dose is accounted for in the feces. [27]
NIASPAN® (niacin extended-release tablets)	Niacin and its metabolites are rapidly eliminated in the urine. [28] Following single and multiple doses, ~60% to 76% of the niacin dose was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Table 1.13 Special Populations (Geriatrics, Pediatrics)

Brand	Geriatrics	Pediatrics
Lovaza® (omega-3-acid ethyl esters), capsules	A limited number of patients over 65 years of age were enrolled in the clinical studies. Safety and efficacy findings in subjects over 60 years of age did not appear to differ from those of subjects less than 60 years of age.[1]	Safety and effectiveness in pediatric patients under 18 years of age have not been established. [1]
ANTARA™ (fenofibrate capsules) micronized	In elderly volunteers 77 to 87 yrs, oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. A similar dosage regimen can be used in the elderly without increasing accumulation of the drug or metabolites.[25,26]	Safety and efficacy have not been investigated in adequate and well-controlled trials in pediatric patients.[25,26]
TRICOR® (fenofibrate tablets)		

LOPID® (gemfibrozil tablets, USP)	Not available.	Safety and efficacy in pediatric patients have not been established. [27]
NIASPAN® (niacin extended-release tablets)	Of 979 patients in clinical studies of NIASPAN®, 21% of the patients were ≥ 65 years. No overall differences in safety and effectiveness were observed between younger patients and those who were [28]	Safety and effectiveness of niacin therapy in pediatric patients (≤ 16 years) have not been established. No studies in patients under 21 years of age have been conducted with NIASPAN®. [28]

Table 1.14 Special Populations (Gender, Race)

Brand	Gender	Race
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available.	Not available.
ANTARA® (fenofibrate capsules) micronized	No pharmacokinetic difference between males and females has been observed for fenofibrate.[25,26]	The influence of race on the pharmacokinetics of fenofibrate has not been studied.[26]
TRICOR® (fenofibrate tablets)		
LOPID® (gemfibrozil tablets, USP)	Not available.	Not available.
NIASPAN® (niacin extended-release tablets)	Steady-state plasma concentrations of niacin and metabolites are higher in women than in men; the magnitude of difference varies with dose and metabolite. However, recovery of niacin and metabolites in urine is similar for both. Gender differences observed in plasma levels of niacin and metabolites may be due to gender differences in metabolic rate or volume of distribution. Data from clinical trials suggest women have a greater hypolipidemic response than men at equivalent doses of NIASPAN®. [28]	Not available.

Table 1.15 Special Populations (Renal Insufficiency, Hepatic Insufficiency)

Brand	Renal Insufficiency	Hepatic Insufficiency
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available.	Not available.
ANTARA® (fenofibrate capsules) micronized	In a study in patients with *severe* renal impairment (creatinine clearance <50 mL/min), the rate of clearance of fenofibrate was greatly reduced resulting in the accumulation of the drug during chronic dosage.[25, 26] However, in patients with *moderate* renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid were increased compared with healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Dosage should be minimized in patients with severe renal impairment, while no modification of dosage is required in patients with moderate renal impairment.	No pharmacokinetic studies have been conducted in patients with hepatic insufficiency.[25, 26]
TRICOR® (fenofibrate tablets)		
LOPID® (gemfibrozil tablets, USP)	Not available.	Not available.
NIASPAN® (niacin extended-release tablets)	There are no data in this population. NIASPAN® should be used with caution in patients with renal disease. [28]	No studies were performed. NIASPAN® should be used with caution in patients with a history of liver disease, who consume substantial quantities of alcohol, or have unexplained transaminase elevations. [28]

Table 1.16 Special Populations (Drug-Drug Interactions)

Brand	**Drug-Drug Interactions**
Lovaza™ (omega-3-acid ethyl esters), capsules	
ANTARA® (fenofibrate capsules) micronized	*In vitro* studies using human liver microsomes indicate fenofibrate and fenofibric acid are not inhibitors of CP450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations. [26] Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR. [26] Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. [26]

TRICOR® (fenofibrate tablets)	*In vitro* studies using human liver microsomes indicate fenofibrate and fenofibric acid are not inhibitors of CP450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations. [25] Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.[25] Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.[25] Concomitant administration of Tricor and pravastatin resulted in no clinically significant difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone. [25]
LOPID® (gemfibrozil tablets, USP)	Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs. [27]
NIASPAN® (niacin extended-release tablets)	

Table 1.17 Contraindications

Brand	Contraindications
Lovaza™ (omega-3-acid ethyl esters), capsules	Patients who exhibit hypersensitivity to any component of the medication.[1]
ANTARA® (fenofibrate capsules) micronized TRICOR® (fenofibrate tablets)	• Hepatic or severe renal dysfunction, including primary biliary cirrhosis, and unexplained persistent liver function abnormality [25, 26] • Pre-existing gallbladder disease [25, 26] • Hypersensitivity to fenofibrate [25, 26]
LOPID® (gemfibrozil tablets, USP)	• Combination therapy with cerivastatin due to the increased risk of myopathy and rhabdomyolysis. [27] • Hepatic or severe renal dysfunction, including primary biliary cirrhosis.[27] • Pre-existing gallbladder disease (see WARNINGS).[27] • Hypersensitivity to gemfibrozil.[27]
NIASPAN® (niacin extended-release tablets)	• Significant or unexplained hepatic dysfunction; active liver disease; unexplained transaminase elevations. [28] • Active peptic ulcer disease. [28] • Arterial bleeding.[28] • Hypersensitivity to niacin or any component of the medication.[28]

Table 1.18 Warnings

Brand	Liver Function	Cholelithiasis	Oral Anti-coagulants	Statins	All cause Mortality	Skeletal Muscle (rhabdo-myolysis)	Cataracts
Lovaza™[1]	← There are no warnings for Lovaza™ →						
ANTARA® (fenofibrate capsules) micronized [26]	√	√	√	√	√	√	
TRICOR® (fenofibrate tablets)[25]	√	√	√	√	√	√	
LOPID® (gemfibrozil tablets, USP)[27]		√	√	√	√	√	√
NIASPAN® (niacin extended-release tablets)[28]	√			√		√	

Table 1.19 Precautions—General: Initial and Continued Therapy

Brand	Initial Therapy	Continued Therapy
Lovaza™ (omega-3-acid ethyl esters), capsules	Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Lovaza™ therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG–lowering drug therapy.[1]	Laboratory studies should be performed periodically to measure the patient's TG levels during Lovaza™ therapy. Lovaza™ therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.[1]
ANTARA® (fenofibrate capsules) micronized TRICOR® (fenofibrate tablets)	Laboratory studies should be done to ascertain lipid levels are consistently abnormal before instituting therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG–lowering drug therapy.[25-27]	Periodic determination of serum lipids should be obtained in order to establish the lowest effective dose. Therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment with the maximum recommended dose.[25, 26]
LOPID® (gemfibrozil tablets, USP)		Periodic determination of serum lipids should be obtained and the drug withdrawn in patients who do not have an adequate response after 3 months of treatment.[27]
NIASPAN® (niacin extended-release tablets)	Attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese	All information from product insert.[28] Patients with history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely.

	patients, and to treat other underlying medical problems closely. [28]	Frequent monitoring of liver function tests and blood glucose. Diabetic or potentially diabetic patients should be observed. Caution should be used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents. Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout. Patients undergoing surgery should be carefully evaluated. Caution should be observed when niaspan is administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients. Phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

Table 1.20 Precautions – Laboratory Tests

Brand	Laboratory Tests
Lovaza™ (omega-3-acid ethyl esters), capsules	In some patients, increases in ALT levels without a concurrent increase in AST levels were observed. ALT levels should be monitored periodically during Lovaza™ therapy. In some patients, Lovaza™ increased LDL-C levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza™ therapy. [1]
ANTARA® (fenofibrate capsules) micronized	Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy, and therapy discontinued if enzyme levels persist above three times the normal limit.[25, 26]
TRICOR® (fenofibrate tablets)	
LOPID® (gemfibrozil tablets, USP)	Abnormal liver function tests have been observed occasionally during LOPID® administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when LOPID® is discontinued. Therefore, periodic liver function studies are recommended and LOPID® therapy should be terminated if abnormalities persist. [27]
NIASPAN® (niacin extended-release tablets)	May produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. May also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests. Liver tests should be performed on all patients during therapy with NIASPAN®. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Patients who develop elevated serum transaminase levels should be monitored; measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued. [28]

Table 1.21 Precautions: Drug Interactions

Brand	Drug Interactions
Lovaza™ (omega-3-acid ethyl esters), capsules	***Anticoagulants***. Omega-3 fatty acids have been shown to potentially cause antithrombotic effects. However, to date, no published studies have demonstrated significant changes in bleeding time or propensity for bleeding among patients treated with FDA-approved doses of Lovaza™. A recent review of the literature on the risk of bleeding associated with omega-3 fatty acids concluded that "the risk of clinically significant bleeding was virtually nonexistent." Although additional blood testing is not required for patients taking approved doses of Lovaza™, patients should be monitored for signs and symptoms of bleeding prior to, and throughout, treatment with Lovaza™.[1] ***Cytochrome P450-Dependent Monooxygenase Activities.*** Omega-3-fatty acid containing products have shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Lovaza™ to induce P450 activities in humans has not been studied. However, since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.[1]
ANTARA® (fenofibrate capsules) micronized TRICOR® (fenofibrate tablets)	***Anticoagulants:*** Exercise caution when administered concomitantly with coumarin anticoagulants. Reduce dosage to maintain prothromin time/INR.[25, 26] ***HMG-CoA Reductase Inhibitors*:** Combined use should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.[25, 26] ***Resins*:** Take fenofibrate at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.[25, 26] ***Cyclosporine:*** Risk that an interaction will lead to deterioration in kidney function.[25, 26]
LOPID® (gemfibrozil tablets, USP)	***HMG-CoA Reductase inhibitors*:** The risk of myopathy and rhabdomyolysis is increased with combined gemfibrozil and HMG-CoA reductase inhibitor therapy. Myopathy or rhabdomyolysis with or without acute renal failure have been reported as early as three weeks after initiation of combined therapy or after several months. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.[27] ***Anticoagulants:*** Exercise caution when administered concomitantly with coumarin anticoagulants. Reduce dosage to maintain prothromin time/INR.[27] ***Repaglinide***: *In vivo* data from a study that evaluated the co-administration of gemfibrozil with repaglinide in healthy subjects resulted in a significant increase in repaglinide blood levels. Patients taking repaglinide should not start taking gemfibrozil; patients taking gemfibrozil should not start taking repaglinide. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide. Caution should be used in patients already on repaglinide and gemfibrozil—blood glucose levels should be monitored and repaglinide dose adjustment may be needed. Rare post marketing events of serious hypoglycemia have been reported in patients taking repaglinide and gemfibrozil together. In this same study, gemfibrozil and itraconazole had a synergistic metabolic inhibitory effect on repaglinide. Therefore, patients taking repaglinide and gemfibrozil should not take itraconazole.[27]
NIASPAN® (niacin extended-release tablets)	***HMG-CoA Reductase Inhibitors:*** Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and NIASPAN® should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.[28] ***Antihypertensive Therapy:*** Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.[28] ***Aspirin:*** Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.[28] ***Bile Acid Sequestrants:*** An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of NIASPAN®.[28]

Table 1.22 Precautions: Geriatric, Pediatric, Cardiovascular

Brand	Geriatric	Pediatric
Lovaza™ (omega-3-acid ethyl esters), capsules	A limited number of patients >65 years were enrolled in clinical studies. In the pooled analyses, safety and efficacy findings in subjects >60 years of age did not appear to differ from those of subjects <60 years.[1]	Safety and efficacy in pediatric patients have not been established.[25, 26]
ANTARA® (fenofibrate capsules) micronized	Fenofibric acid is known to be substantially excreted by the kidney; therefore, the risk of adverse reactions to this drug may be greater in patients with impaired renal function.[25, 26] Elderly patients are more likely to have decreased renal function, so care should be taken in dose selection.	
TRICOR® (fenofibrate tablets)		
LOPID® (gemfibrozil tablets, USP)	Not available.	
NIASPAN® (niacin extended-release tablets)	Clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. [28]	

Table 1.23 Precautions – Carcinogenesis, Mutagenesis, Impairment of Fertility

Brand	Carcinogenesis , Mutagenesis, Impairment of Fertility
Lovaza™ (omega-3-acid ethyl esters), capsules	No evidence of carcinogenicity, mutagenicity or impairment of fertility seen in animal studies.[1]
ANTARA® (fenofibrate capsules) micronized	Evidence of carcinogenesis seen in animal studies only. [25-27]
TRICOR® (fenofibrate tablets)	
LOPID® (gemfibrozil tablets, USP)	
NIASPAN® (niacin extended-release tablets)	No studies have been conducted regarding carcinogenesis, mutagenesis, or impairment of fertility. [28]

Table 1.24 Precautions: Kidney, Cardiovascular

Brand	Kidney Function	Cardiovascular
Lovaza® (omega-3-acid ethyl esters), capsules	Not available	Not available
ANTARA® (fenofibrate capsules) micronized	Not available	Not available
TRICOR® (fenofibrate tablets)	Not available	Not available
LOPID® (gemfibrozil tablets, USP)	Reports of worsening renal insufficiency on addition of LOPID® in individuals with baseline plasma creatinine >2.0 mg/dL. In such patients, alternative therapy should be considered against the risks and benefits of a lower dose of LOPID®.[27]	N/A
NIASPAN® (niacin extended-release tablets)	Niacin is excreted through the kidneys; should be used with caution in patients with renal dysfunction.[28]	Caution advised when used in patients with unstable angina or in the acute phase of MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.[28]

Table 1.25 Precautions: Pancreatitis, Hypersensitivity Reactions

Brand	Pancreatitis	Hyper-Sensitivity Reactions
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available	Caution advised when used in patients with known sensitivity or allergy to fish.[1]
ANTARA® (fenofibrate capsules) micronized	Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This may represent: (1) a failure of efficacy in patients with severe hyper-triglyceridemia, (2) a direct drug effect, or (3) a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.[25, 26]	Acute hypersensitivity reactions (including severe skin rashes requiring patient hospitalization and treatment with steroids) have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1% vs 0%, and rash in 1.4% vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.[25, 26]
TRICOR® (fenofibrate tablets)		
LOPID® (gemfibrozil tablets, USP)	Not available	Not available
NIASPAN® (niacin extended-release tablets)	Not available	Not available

Table 1.26 Precautions: Hematologic Changes, Skeletal Muscle

Brand	Hematologic Changes	Skeletal Muscle
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available	Not available
ANTARA® (fenofibrate capsules) micronized TRICOR® (fenofibrate tablets)	Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the US. Periodic blood counts are recommended during the first 12 months of administration. [25, 26]	Use of fibrates alone may occasionally be associated with myopathy. Treatment with fibrate drugs has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of CPK. [25, 26] Patients should be advised to report promptly of any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed. [25, 26]
LOPID® (gemfibrozil tablets, USP)	Mild hemoglobin, hematocrit, and white blood cell decreases have been observed in occasional patients following initiation of LOPID® therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Periodic blood counts are recommended during the first 12 mos of LOPID® administration. [27]	Concomitant therapy with statins are associated with an increased risk of skeletal muscle toxicity manifested as rhabdomyolysis, markedly elevated creatine kinase levels and myoglobinuria leading to acute renal failure and death. [27]
NIASPAN® (niacin extended-release tablets)	NIASPAN® has been associated with small but statistically significant dose-related reductions in platelet count (mean reduction of 11% with 2000 mg). It has also been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%). Accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely. [28]	Rare cases of rhabdomyolysis have been associated with concomitant administration of niacin (≥ 1 g/day) and statins.[28]

Table 1.27 Precautions: Other

Brand	Other Precautions
Lovaza™ (omega-3-acid ethyl esters), capsules	Not available
ANTARA® (fenofibrate capsules) micronized	Not available
TRICOR® (fenofibrate tablets)	Not available
LOPID® (gemfibrozil tablets, USP)	Abnormal liver function tests have been observed occasionally during LOPID® administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when LOPID® is discontinued. Therefore, periodic liver function studies are recommended and LOPID® therapy should be terminated if abnormalities persist. [27]
NIASPAN® (niacin extended-release tablets)	All information from product insert.[28] • Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely. • Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. • Diabetic patients may experience a dose-related rise in glucose intolerance, the clinical significance of which is unclear. • Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary. • Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout. • NIASPAN® has been associated with small but statistically significant dose-related reductions in platelet count (mean of −11% with 2000 mg). • NIASPAN® has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated.

Table 1.28 Precautions - Pregnancy and Nursing Mothers

Brand	Pregnancy Category C	Nursing Mothers
Lovaza™ (omega-3-acid ethyl esters), capsules	Evidence of adverse effects seen in animal studies only.[1, 25-27] No adequate and well-controlled studies in pregnant women. Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	Unknown whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovaza™ is administered to a woman who is breastfeeding.[1]
ANTARA® (fenofibrate capsules) micronized		Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.[25, 26]
TRICOR® (fenofibrate tablets)		
LOPID® (gemfibrozil tablets, USP)		Unknown whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for LOPID® in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.[27]
NIASPAN® (niacin extended-release tablets)	Animal reproduction studies have not been conducted. It is unknown if niacin used for lipid disorders can cause fetal harm when given to pregnant women or if can affect reproductive capacity. Women receiving niacin for primary hyper-cholesterolemia (Types IIa, IIb) who become pregnant should discontinue drug. If woman treated with niacin for HTG (Types IV or V) conceives, the benefits and risks of continued therapy should be assessed.[28]	Reported to be excreted in human milk. Due to potential for serious adverse reactions in nursing infants from lipid-altering doses, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother. No studies have been conducted in nursing mothers.[28]

Table 1.29 Adverse Effects

Brand	Adverse Effects

Lovaza™ (omega-3-acid ethyl esters), capsules

BODY SYSTEM Adverse Event	LOVAZA (N = 226) n	%	Placebo* (N = 228) n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive Dyspepsia Eructation		3.1		2.6
	7 11	4.9	6 5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.[1]
*Placebo was corn oil for all studies.

ANTARA®
(fenofibrate capsules) micronized[26]

TRICOR®
(fenofibrate tablets)[25]

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4%**	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 130 mg Antara
** Significantly different from Placebo

Adverse Effects (Continued)

<table>
<tr><th>Brand</th><th>Adverse Effects</th></tr>
<tr><td>LOPID®
(gemfibrozil tablets, USP)[27]</td><td>
<table>
<tr><th></th><th>LOPID
(N = 2046)</th><th>PLACEBO
(N = 2035)</th></tr>
<tr><th></th><th colspan="2">Frequency in percent of subjects</th></tr>
<tr><td>Gastrointestinal reactions</td><td>34.2</td><td>23.8</td></tr>
<tr><td>Dyspepsia</td><td>19.6</td><td>11.9</td></tr>
<tr><td>Abdominal pain</td><td>9.8</td><td>5.6</td></tr>
<tr><td>Acute appendicitis</td><td>1.2</td><td>0.6</td></tr>
<tr><td>(histologically confirmed in most cases where data were available)</td><td></td><td></td></tr>
<tr><td>Atrial fibrillation</td><td>0.7</td><td>0.1</td></tr>
<tr><td colspan="3">Adverse events reported by more than 1% of subjects, but without a significant difference between groups:</td></tr>
<tr><td>Diarrhea</td><td>7.2</td><td>6.5</td></tr>
<tr><td>Fatigue</td><td>3.8</td><td>3.5</td></tr>
<tr><td>Nausea/Vomiting</td><td>2.5</td><td>2.1</td></tr>
<tr><td>Eczema</td><td>1.9</td><td>1.2</td></tr>
<tr><td>Rash</td><td>1.7</td><td>1.3</td></tr>
<tr><td>Vertigo</td><td>1.5</td><td>1.3</td></tr>
<tr><td>Constipation</td><td>1.4</td><td>1.3</td></tr>
<tr><td>Headache</td><td>1.2</td><td>1.1</td></tr>
</table>
</td></tr>
<tr><td>NIASPAN®
(niacin extended-release tablets)[28]</td><td>
<table>
<tr><th></th><th></th><th></th><th colspan="3">Recommended Daily Maintenance Doses</th><th colspan="2">Greater Than Recommended Daily Doses</th></tr>
<tr><th></th><th>Placebo (n=157) %</th><th>500mg‡ (n=87) %</th><th>1000mg (n=110) %</th><th>1500mg (n=136) %</th><th>2000mg (n=95) %</th><th>2500mg‡ (n=49) %</th><th>3000 mg‡ (n=46) %</th></tr>
<tr><td>Headache</td><td>15</td><td>5*</td><td>9</td><td>11</td><td>8</td><td>4*</td><td>4</td></tr>
<tr><td>Pain</td><td>3</td><td>1</td><td>2</td><td>5</td><td>3</td><td>0</td><td>2</td></tr>
<tr><td>Pain, Abdominal</td><td>3</td><td>3</td><td>2</td><td>3</td><td>5</td><td>0</td><td>0</td></tr>
<tr><td>Diarrhea</td><td>8</td><td>6</td><td>7</td><td>6</td><td>8</td><td>10</td><td>11</td></tr>
<tr><td>Dyspepsia</td><td>8</td><td>2</td><td>4</td><td>5</td><td>5</td><td>6</td><td>0</td></tr>
<tr><td>Nausea</td><td>4</td><td>2</td><td>5</td><td>3</td><td>8</td><td>10</td><td>4</td></tr>
<tr><td>Vomiting</td><td>2</td><td>0</td><td>2</td><td>3</td><td>8*</td><td>8</td><td>2</td></tr>
<tr><td>Rhinitis</td><td>7</td><td>2</td><td>5</td><td>4</td><td>3</td><td>0</td><td>0</td></tr>
<tr><td>Pruritus</td><td>1</td><td>6</td><td><1</td><td>3</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Rash</td><td><1</td><td>5</td><td>5</td><td>4</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
</table>

Note: Percentages are calculated from the total number of patients in each column. AEs are reported at the lowest dose where they occurred.
† Pooled results from placebo-controlled studies; for NIASPAN®, n=245 and mean treatment duration = 17 weeks. Number of NIASPAN® patients (n) are not additive across doses.
‡ The 500mg, 2500mg and 3000mg/day doses are outside the recommended daily maintenance dosing range; see **DOSAGE AND ADMINISTRATION**.
* Significantly different from placebo at $P \leq .05$; Chi-square test (cell sizes >5), Fisher's Exact test (cell sizes ≤5).

2.0 PLACE IN THERAPY

2.1 Epidemiology and Relevant Risk Factors for Hypertriglyceridemia

Hypertriglyceridemia is defined as an elevation of TGs in serum or plasma. Elevated TGs are now considered as an independent risk factor for CHD [29, 30]After reviewing the recent evidence, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) has concluded that the link between serum TG and CHD is stronger than previously recognized. [2]

Hypertriglyceridemia is commonly associated with the highly atherogenic lipid triad: an increase in large VLDL particles, a reduction in large HDL-C particles, and increased levels of small dense LDL-C. [31]This lipid triad may also be referred to as diabetic dyslipidemia as it is often associated with insulin resistance. In fact, an increased TG:HDL-C ratio might be considered the single most characteristic feature of insulin resistance, being more predictive than the presence of abdominal obesity. The most common causes of HTG are overweight/obesity and lack of physical activity. Other contributing factors of hypertriglyceridemia HTG include

- Cigarette smoking
- Excess alcohol intake
- Very high-carbohydrate diets (>60% of total energy)
- Other diseases (type 2 diabetes, chronic renal failure, nephritic syndrome
- Certain drugs (corticosteroids, protease inhibitors for HIV, beta-adrenergic blocking agents, estrogens)
- Genetic factors

The ATP III classifications of serum TG levels are listed in Table 2.1.[2]

Table 2.1 ATP III Classification of Serum Triglycerides [2]

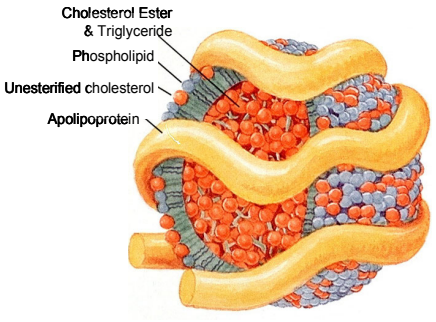
Category	Level
Normal trigylcerides	<150 mg/dL
Borderline-high triglycerides	150-199 mg/dL
High triglycerides	200-499 mg/dL
Very high triglycerides	≥500 mg/dL

An estimated 13% of the US population meets criteria for high TG levels, and approximately 3% meets criteria for very high TG levels (derived from data provided by NCEP ATP III). Importantly, when TG levels are 500 mg/dL or greater, ATP III guidelines state that hypertriglyceridemia should be treated first and LDL-C levels optimized thereafter.

2.2 Pathophysiology of Hypertriglyceridemia

Lipid Metabolism

Figure 2.1 Composition of Lipoproteins



Four major types of lipids circulate in plasma: cholesterol, cholesteryl esters, phospholipids, and TGs.[32] Triglycerides—composed of a glycerol molecule covalently linked to three fatty acid chains—are the primary transport and storage form of lipids in the body; fatty acids released from TG are used for energy. Cholesterol is a lipid that is present in cell membranes and is a precursor of bile acids and steroid hormones. Most plasma cholesterol circulates in the form of cholesteryl esters, with a fatty acid linked to its hydroxyl group'

Lipoproteins are comprised of a hydrophobic core of cholesteryl esters and TGs, an outer monolayer of phospholipids and unesterified cholesterol, and finally protein ligands (apoproteins) that wrap around the outside of the particle (Figure 2.1). Apoproteins provide structural integrity to the lipoproteins and regulate their functions including receptor-specific binding, lipid transfer, and lipolysis. Lipoproteins vary in size, lipid composition, and apoprotein makeup, and are classified as VLDL, LDL, HDL, and chylomicrons. [32]

The properties of these plasma lipoproteins are provided below (Table 2.2).

Table 2.2 Properties of Plasma Lipoproteins *(Adapted from McKenney)* [32]

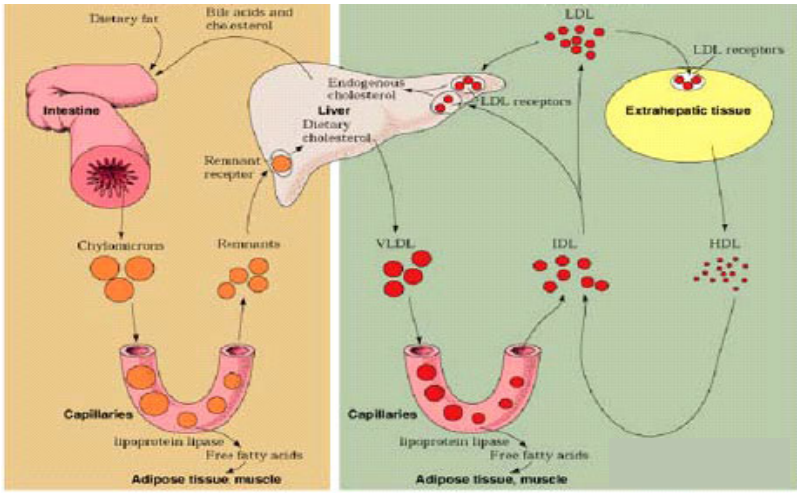
Properties	VLDL	LDL	HDL	Chylomicron
Density (g/mL)	0.94 – 1.006	1.006 – 1.063	1.063-1.210	<0.94
Composition %				
Protein	6-10	18-22	45-55	1-2
Triglyceride	50-65	4-8	2-7	85-95
Cholesterol	20-30	51-58	18-25	3-7
Phospholipid	15-20	18-24	26-32	3-6
Physiologic Origin	Liver and intestine	VLDL catabolism	Liver and intestine	Intestine
Physiologic Function	Transport endogenous TG and cholesterol	Transport endogenous cholesterol to cells	Transport cholestrol from cells to liver	Transport dietary cholesterol and TG to liver
Plasma Appearance	Turbid	Clear	Clear	Cream layer
Apolipoproteins	B-100, C-IC-III, C-III, E	B-100, (a)	A-I, A-II, A-IV	A-IV, B-48, C-IC-II, C-III

Chylomicrons are large, TG-rich lipoproteins. As they transport dietary fatty acids and cholesterol (exogenous lipids) from the gut to the liver, some of the fatty acids are cleaved from TG by lipoprotein lipase. Chylomicrons peak after a meal and are usually catabolized within 10 to 12 hours. Because serum lipid profiles are focused on the measurement of TG that are produced in the liver (rather than those

derived from diet), patients are usually asked to fast before lipid measurements to allow for chylomicron clearance.[32]

Exogenous *Endogenous*

Figure 2.2 Endogenous and Exogenous Cholesterol Transport



In the liver, endogenous lipids and those from dietary sources are packaged into VLDL particles, which contain TG as the main component. As VLDL particles circulate in the bloodstream, some of the TG content is hydrolyzed by lipoprotein lipase (LPL) and endothelial lipase (EL) to release free fatty acids that are essential for metabolic activity. The remnants of VLDL particles, including intermediate-density lipoprotein (IDL), are smaller and enriched in cholesterol. Approximately half of VLDL remnants are removed from systemic circulation by LDL-C receptors present on the surface of the liver, while the remaining particles undergo further lipolysis to be transformed into LDL-C (Figure 2.2). Because IDL and LDL are produced from VLDL, both particles contain Apo B100 as their primary apolipoprotein.[32]

Low-density lipoproteins are heterogeneous in size, density, and composition and typically carry the majority (60-70%) of plasma cholesterol. Approximately half of LDL-C particles are removed from systemic circulation by binding to LDL-C receptors on the liver, while the rest can be taken up by peripheral tissues, including the arterial wall.[32] Clinical studies as well as animal and *in vitro* data suggest that small and dense LDL-C particles are more atherogenic when compared with the large and more buoyant particles. [30, 33, 34]

High-density lipoprotein (HDL) particles are the smallest of lipoproteins (25% cholesterol and 5% to 10% TG) and have high apolipoprotein content. HDL particles transport cholesterol from peripheral cells back to the liver—a process called reverse cholesterol transport—the mechanism by which cholesterol is removed from the arterial wall. HDL particles are heterogeneous in size; the smaller HDL_3 is converted to larger HDL_2 as it acquires TG and cholesterol from peripheral cells and circulating lipoproteins. Conversely, HDL_2 particles undergo lipolysis to HDL_3 through the action of hepatic lipase.[32]

Hypertriglyceridemia and the Atherogenic Lipid Triad

Non–HDL cholesterol refers to the combined amount of cholesterol carried by VLDL and LDL particles; non–HDL-C is determined by subtracting HDL-C level from TC. ATP III guidelines have established the

lowering of non–HDL-C as a secondary goal in lipid management. High TG levels drive the assembly and release of very large VLDL particles that have increased plasma residence time. Recent studies suggest that such TG-rich particles are 5 times more susceptible (relative to LDL-C) to remodel the arterial wall, leading to pro-atherogenic particle aggregation and retention. [35]

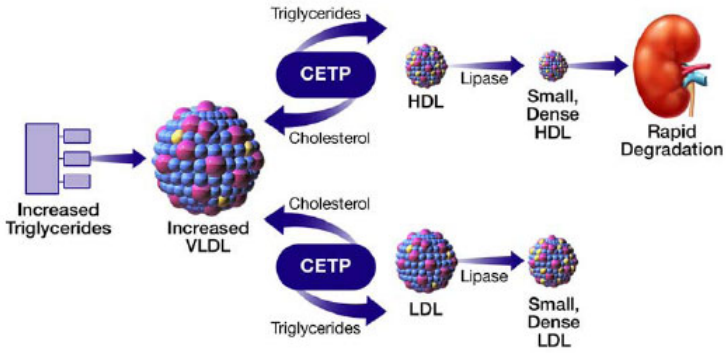


Figure 2.3 Elevated TG levels drive the atherogenic lipid triad

The production of larger VLDL particles with High TG content also drive the transfer of lipids between lipoproteins. Specifically, cholesteryl ester transfer protein (CETP), an enzyme that exchanges cholesterol and TG between lipoproteins, transfers TG from VLDL to LDL with the concomitant movement of cholesteryl esters from LDL to VLDL. The resulting TG-enriched and cholesterol-depleted LDL particles undergo lipolysis to be converted into small, dense LDL particles, whereas VLDL particles become cholesterol enriched. Similar to the reaction with LDL, CETP may also act on HDL particles and enable the transfer of cholesterol from HDL to VLDL, and TG from VLDL to HDL (Figure 2.3).[36]

The high TG-driven shift to smaller HDL particles is known to be atherogenic for 2 reasons. First, small HDL particles are more readily removed from plasma resulting in an overall decrease in HDL-C levels. Second, large HDL particles are better at removing cholesterol from peripheral tissues, and therefore a shift from large HDL results in decreased cholesterol removal from the arterial wall. It is interesting that even modest elevations in fasting TG levels can result in significant TG enrichment of HDL-C. [37]

It is important to note that hypertriglyceridemic patients do not typically have high LDL-C levels, which is due to at least 2 factors. First, longer plasma residence time of large VLDL particles would slow the conversion into LDL particles. Second, the transfer of cholesterol from LDL-C to VLDL (via increased CETP-mediated lipid exchange) leads to lower LDL-C levels. Hypertriglyceridemic patients do, however, have high non–HDL-C levels (due to high VLDL), and a higher fraction of atherogenic sdLDL.[38] The sdLDL particles are more atherogenic than the lighter fractions. Poor recognition by the LDL receptor-mediated clearance mechanism allows them to stay in the plasma compartment for longer and thereby penetrate the arterial intimae more readily. Within the arterial intimae, sdLDL particles are readily oxidized, which leads to increased uptake by macrophage cells and their subsequent conversion to foam cells – a characteristic marker of the atherosclerotic plaque. [39]

In summary, high TG levels create a lipid profile consisting of TG-rich VLDL, loss of large HDL, and increased numbers of sdLDL particles.[40] In other words, hypertriglyceridemia induces the highly atherogenic lipid triad that is associated with an increased risk for MI and coronary artery disease.[40]

2.3 Clinical Presentation

Hypertriglyceridemia and the Development of Pancreatitis

Patients with TG levels greater than 1000 mg/dL are at high risk of developing pancreatitis.[2] Of 1193 patients reported with acute pancreatitis in Taiwan between 1998 and 2000, the etiology in 12% of patients was identified as hypertriglyceridemia.[41] Mortality rates in the first month following onset are approximately 30 times higher than rates among the general population of equivalent age.[42]

Hypertriglyceridemia as an Independent Risk Factor for Atherogenesis and CHD

Hypertriglyceridemia is the primary focus of lipid therapy when TG levels are over 500 mg/dL, and a secondary target when TG levels are under 500 mg/dL (ATP III guidelines). As discussed in section 2.2, elevated TG levels are closely linked to concurrent changes in TC, LDL-C, and HDL-C levels. In a meta-analysis of 17 population-based studies reporting the association between fasting TG levels and CVD endpoints among 46,413 men and 10,864 women, it was found that an increase in serum TG levels by 88 mg/dL was associated with a 14% increased risk for CHD in men, and a 37% increased risk for women. These findings were recently updated in a new study that included more than 75,000 subjects.[43] The authors reported that an increase of 39 mg/dL in TG levels significantly predicted a 12% increase in CVD risk in men and a 37% increase in women. These risks were apparent even after adjusting for HDL-C and other risk factors for CVD.

Data from the Copenhagen Male study, an 8-year follow-up of nearly 3000 men, reported a statistically significant and an independent effect for increased TG levels on ischemic heart disease.[44] Similarly, the Bezafibrate Infarction Prevention (BIP) study, a 5-year follow-up of more than 9000 men and nearly 2500 women, showed an unadjusted mortality risk of 77% for men and 200% for women with TG levels exceeding 217 mg/dL.[45] Notably, mortality was elevated in patients with high TG levels even among those who had desirable TC and LDL-C levels, and desirable or low HDL-C levels.

Data from the Framingham Heart Study reported a linear relationship between serum TG levels and the subsequent development of CHD (Figure 2.4). The increase in CHD was significantly evident in men and women with high TG levels (>150 mg/dL) and low HDL-C levels (<40 mg/dL).[46] Because these patients had total cholesterol levels at or below 200 mg/dL, it is likely those at risk may have been overlooked by standard cholesterol screening programs.

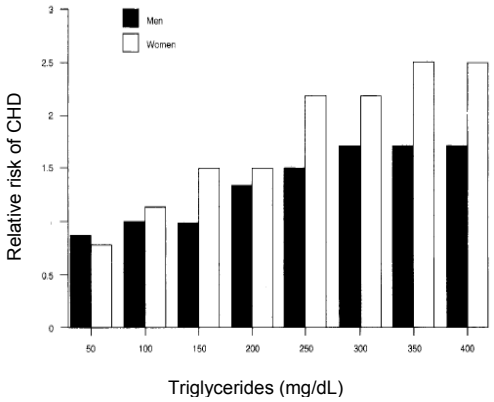


Figure 2.4 Relative risk of Coronary artery disease by serum TG levels in men and women (30 year follow-up).

Adapted from Castelli WP, 1992.

Prospective studies among first-degree relatives of patients with familial forms of hypertriglyceridemia demonstrated a strong association between TG levels and premature CAD,[47, 48] and CVD mortality.[49]

In the Prospective Cardiovascular Munster (PROCAM) Study, 4849 middle-aged men were followed up

for 8 years and the incidences of CHD were recorded. Investigators found that incidence of CHD events rose with increasing TG levels within each LDL-C subgroup.[29] For example, the incidence of CHD events in subjects who had high serum TG levels (≥200 mg/dL) and high LDL-C levels (≥190 mg/dL) at baseline were more than twice that of subjects with lower TG levels (<200 mg/dL) and high LDL-C levels: 255 events/1000 individuals vs 107 events/1000 individuals. This synergistic relationship between raised TG levels and LDL-C, and its correlation to CHD risk was apparent at all concentrations of LDL-C (Figure 2.5).

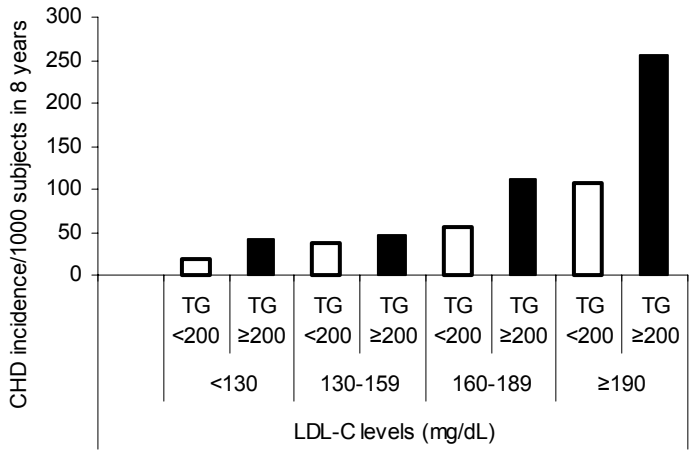


Figure 2.5 Incidence of coronary heart disease events according to serum LDL-C and TG levels; data from PROCAM study

Adapted from Assmann et al., 1998.

Relative risk of coronary disease among those with TG levels >400 mg/dL was 2.5 times higher compared with those whose levels were <150 mg/dL; the risk increased significantly even when TG levels were <200 mg/dL (Figure 2.6)[50].

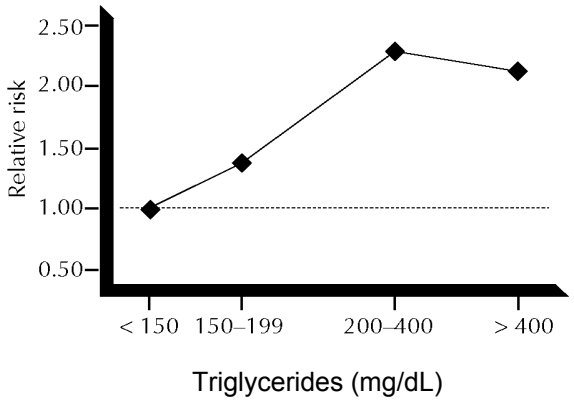


Figure 2.6 Relative risk of coronary disease based on TG categories derived from 8-year cumulative incidence data from PROCAM study

A relative risk of 1.0 is denoted by a horizontal dotted line and represents no association.

Adapted from Hokanson et al., 2002.

Hopkins et al examined the independent contribution of elevated TG levels to CAD risk.[51]Serum lipids were analyzed in 653 patients with premature familial CAD and in 1029 control subjects; the risk was stratified by TG levels as shown below in Table 2.3 and Figure 2.7. Patients with TG levels between 500 mg/dL and 799 mg/dL had a 14.8-fold increased risk of developing CAD (minimally adjusted model)

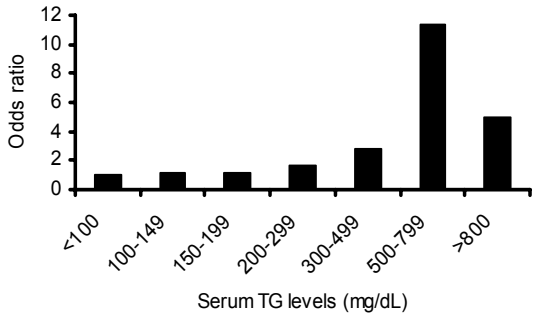
compared with patients with TG levels below 100 mg/dL. This risk persisted even after adjusting for HDL-C and other elements of the metabolic syndrome and CAD risk factors.

Table 2.3 Independent Contribution of Elevated TG to CAD Risk [51]

	N in Category (Cases, Control Subjects)	Minimally Adjusted Model*		Fully Adjusted Model*	
		OR (95% CI)	p Value	OR (95% CI)	p Value
Triglyceride categories					
<100 mg/dl	89, 284	1.0 (–)	—	1.0 (–)	—
100–149 mg/dl	171, 325	1.5 (1.04–2.1)	0.030	1.2 (0.81–1.8)	0.34
150–199 mg/dl	386, 420	1.8 (1.2–2.6)	0.0027	1.1 (0.70–1.7)	0.72
200–299 mg/dl	144, 150	1.9 (1.3–2.7)	0.0011	1.7 (1.1–2.6)	0.012
300–499 mg/dl	74, 49	3.8 (2.3–6.3)	<0.0001	2.8 (1.6–4.9)	0.0003
500–799 mg/dl	19, 7	14.8 (5.3–41.6)	<0.0001	11.4 (3.4–38.0)	<0.0001
800+ mg/dl	2, 1	33.0 (2.9–332)	0.0051	5.0 (0.29–85.1)	0.27
Type III hyperlipidemia	22, 10	5.2 (2.0–13.8)	0.0008	5.4 (1.9–15.4)	0.0016

Figure 2.7 Serum TG levels and the relative risk of developing CHD

Adapted from Hopkins et al 2005.



Treatment of hypertriglyceridemia reduces the risk for atherogenesis and CHD. The Helsinki Heart Study[52]: a 5-year randomized, double-blind, placebo-controlled trial of gemfibrozil versus placebo in 4081 middle-aged dyslipidemic men. The primary endpoints were fatal and nonfatal MI and cardiac death. During the 5-year period, patients treated with gemfibrozil (600 mg twice daily) experienced a 35% reduction in TG levels (baseline 175.3 mg/dL) and a 34% reduction in fatal and nonfatal MI and cardiac death.

The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[53]: a 5-year, randomized, double blind, placebo-controlled, secondary prevention trial was designed to test the efficacy of gemfibrozil on CVD endpoints; the primary endpoint was death from CHD or nonfatal MI. Treatment with gemfibrozil 1200 mg/day significantly reduced TG levels by 31% (baseline: 160 mg/dL) and increased HDL-C by 6% (baseline: 32 mg/dL) with minimal effect on LDL-C levels. Significant reductions were also found in the primary endpoint (-22%) and in the combined outcome of death, nonfatal MI, and stroke (-24%).

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study[54]: a 5-year, multinational,

randomized, placebo-controlled trial to evaluate the effects of fenofibrate on CV events in 9795 patients with type 2 diabetes. The primary endpoint was the incidence of coronary events (CHD death or nonfatal MI). Although fenofibrate therapy (micronised 200 mg/d) did not significantly reduce the total incidence of coronary events (Hazard Ratio [HR] 0.89, 95% CI 0.75-1.05; *P* = .16), significant reductions were found in nonfatal MI (HR 0.76, 95% CI 0.62-0.94; *P* = .010), total CV events (HR 0.89, 95% CI 0.80-0.99; *P* = .035) and coronary revascularization (HR 0.79, 95% CI 0.68-0.93; *P* = .003). At study close, decreases were found in the levels of TG (-21.9%: baseline 174 mg/dL), LDL-C (-5.8%: baseline 120 mg/dL), and TC (-6.9%: baseline 197 mg/dL) whereas, HDL-C level increased by 1.2% (baseline: 42.9 mg/dL).

The Coronary Drug Project[55]: a 5-year, randomized, double blind, placebo-controlled study to assess the safety and efficacy of niacin (3 g/day) and clofibrate (1.8 g/day) in 8341 men aged between 30 and 64 years with a history of MI. The primary endpoint was total mortality, and secondary endpoints were coronary mortality, sudden death and other nonfatal CV events. Total mortality was similar in the niacin and placebo groups at 5 years: 24.4% versus 25.4%, respectively. However, niacin was associated with a significant reduction in the 5-year incidence of nonfatal, recurrent MI (-27%; *P* < .004). Treatment with clofibrate and niacin resulted in significant reductions in total cholesterol (-6.5% and -9.9%, respectively) and TG (-22.3% and -26.1%, respectively) from baseline levels.

The Cholesterol-Lowering Atherosclerosis (CLAS) Study[56]: a randomized, placebo-controlled, angiographic trial to evaluate the efficacy of combined colestipol (30 g/d) and niacin (3-12 g/d) therapy in 162 non-smoking males with a history of previous coronary bypass surgery. The primary endpoint was global changes in the score of coronary arteries (a panel of expert angiographers graded changes in grafts and native coronary arteries using a 4-point scale). After 2 years, 61% of patients in the placebo group showed disease progression in both native arteries and grafts compared with 38.8% of patients treated with combined drug therapy (*P* < .005); disease regression also occurred more frequently in the drug-treated group (16.2% versus 2.4%; *P* = .002). After drug therapy significant decreases were found in total cholesterol (-26%: baseline 246 mg/dL), TG (-22%: baseline 151 mg/dL), LDL-C (-43%: baseline 171 mg/dL) and an increase in HDL-C levels (37%: baseline 44.6 mg/dL).

The Familial Atherosclerosis Treatment (FATS) Study[57]: Patients, aged ≤62 years, with established CAD and family history of vascular disease were randomly assigned to one of the following three treatment groups. Treatment groups were niacin (1 g 4 times/day at 2 months) and colestipol (10 g 3 times daily), lovastatin (20 mg twice daily) and colestipol, or conventional therapy (double placebo or placebo plus colestipol if LDL-C was elevated). Patients received double-blind treatment for 2.5 years. The primary endpoint was change in severity of disease in the proximal coronary arteries by quantitative arteriography. Treatment with niacin+colestipol combination resulted in a significant reduction in TG levels (-29.2%: baseline 195 mg/dL) compared with those administered with lovastatin+colestipol therapy (-8.8%: baseline 202 mg/dL). In the conventional therapy group, 46% of patients had disease progression (and no regression) in at least 1 of 9 proximal coronary segments; regression was the only change in 11%. In the niacin+colestipol group, progression (as the only change) was seen in 25% of patients, while regression was observed in 39%. Clinical events (death, MI, or revascularization for worsening angina) occurred in 10 of 52 patients who received conventional therapy, compared with 2 of 48 patients who received niacin +colestipol.

The Harvard Atherosclerosis Reversibility Project (HARP)[58]: a randomized, placebo-controlled, 2.5-year study to evaluate the effect of antihyperlipidemic drug regimen in patients (80 men and 11 women) with CHD; baseline TC <250 mg/dL and ratio of TC:HDL-C >4.0. Drug treatment consisted of an HMG-CoA reductase inhibitor administered alone as an initial therapy followed by addition of varying doses of slow-release nicotinic acid, cholestyramine, or gemfibrozil. Treatment with pravastatin (40 mg/d) resulted in significant decreases in TC (- 22%), LDL-C (-32%), and TG levels (-15%), and increased HDL-C levels (8%; *P* < .001 for all comparisons). Pravastatin also decreased TC: HDL-C by 28% (*P* < .001) and LDL-C: HDL-C by 37% (*P* < .001). The addition of 1.5 g/d of nicotinic acid resulted in further reductions in the

levels of TC (-6%, *P* < .002), LDL-C (-11%, *P* < .001), and TG (-10%, *P* < .001), whereas an additional increase was noted in HDL-C levels (8%, *P* < .001).

2.4 Treatment Approaches for Triglyceride Levels ≥500 mg/dL

In general, the ATP III panel recommended a 2-step approach for the management of cholesterol: reduction of LDL-C levels as the primary target of cholesterol-lowering therapy and thereafter the management of other lipid risk factors, such as elevated TG levels and non–HDL-C levels.[2] However, in patients with TG levels ≥500 mg/dL, TG reduction should be considered as the primary target of treatmentATP III recognized that statins are not powerful TG-lowering drugs, and therefore recommended the specific use of TG-lowering drugs (Figure 2.8). Prior to the availability of Lovaza™, these included fibrates and nicotinic acid.

Table 2.4 ATP III Treatment Considerations for Elevated Serum Triglycerides [2]

Very High Triglycerides (≥500 mg/dL)	■ Goals of therapy: – Triglyceride lowering to prevent acute pancreatitis (first priority) – Prevention of CHD (second priority) ■ Triglyceride lowering to prevent pancreatitis: – Very low-fat diet when TG >1000 mg/dL (<15% of total calories as fat) – Medium-chain triglycerides when TG >1000 mg/dL (can replace long-chain triglycerides in diet) – Institute weight reduction/physical activity – Fish oils (replace some long-chain triglycerides in diet) – Triglyceride-lowering drugs (fibrate or nicotinic acid): most effective – Statins: not first-line agent for very high triglycerides (statins not powerful triglyceride-lowering drugs) – Bile acid sequestrants: contraindicated—tend to raise triglycerides ■ Triglyceride lowering to prevent CHD: – Efficacy of drug therapy to prevent CHD in persons with very high triglycerides not demonstrated by clinical trials

2.5 Drug and Non-drug Treatment Options for TG Levels ≥500 mg/dL

Non-drug Treatment Options

For patients with high TG levels the use of therapeutic lifestyle changes, including lipid-lowering diet and increased level of physical activity may achieve the therapeutic goal.[2] However, diet and lifestyle changes alone are insufficient to achieve TG reduction for many.

Drug Treatment Options

For patients with TG levels ≥500 mg/dL, statins alone are insufficient to reduce TG levels and raise HDL-C. Treatment options include omega-3-acid ethyl esters, fibric acid derivatives, and nicotinic acid either as monotherapy or in combination with statins.[2]

Omega-3-acid ethyl ester

Lovaza™ is the only omega-3-derived prescription pharmaceutical product available in the US.[59] Lovaza™ is a 90% omega-3 product derived from natural marine origin; it consists of 465 mg (46.5%) of eicosapentanoic acid (EPA) ethyl ester, 375 mg (37.5%) docosahexaenoic acid (DHA), and

approximately 80 mg (8%) of other omega-3-acid ethyl esters (Figure 2.9).[1]Non-omega-3 ingredients include 30 mg (3%) of omega-6 acid ethyl esters and other ingredients (5%), including 4 mg of α-tocopherol (vitamin E), gelatine, glycerol and purified water (components of the capsule shell).[1]

Omega-6 and omega-3 fatty acids compete for metabolic conversion to prostaglandins. Omega-6 derived prostaglandins are potent stimulators of inflammation and vasoconstriction, whereas omega-3 derived prostaglandins are not. Thus, high levels of omega-3 fatty acids (92%) and low levels of omega-6 fatty acids (3%) in Lovaza™ are desirable. Given that EPA and DHA have been established as the omega-3-fatty acids that confer the health benefits of fish oil, high levels of these two fatty acids (84%) in Lovaza™ are therapeutically beneficial. [60]

To determine the optimal dosing of Lovaza™ for the reduction of TG, a double-blind, randomized study was conducted.[61] Patients with TG levels between 177 mg/dL and 442 mg/dL were randomized to receive Lovaza™ at doses of 2, 4 or 8 g/day, or placebo for 8 weeks. Significant reductions were found in TG levels from baseline in patients treated with 4 g/day or 8 g/day of Lovaza™ (Figure 2.10).

Figure 2.9 Composition of Lovaza™ [1]

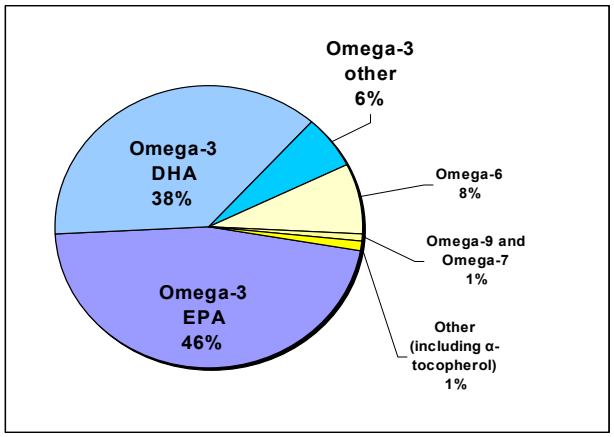
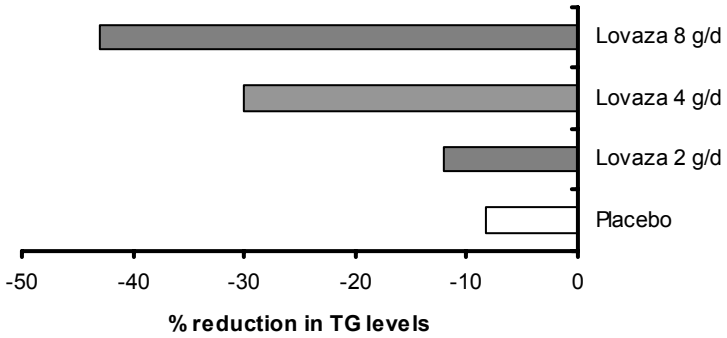


Figure 2.10 Dosing Study Results



The mechanisms of action for TG reduction by Lovaza™ are not completely understood. Potential mechanisms include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Lovaza™ may reduce the synthesis of TG in the liver because EPA and DHA

are poor substrates for the enzymes responsible for the TG synthesis; in addition, EPA and DHA inhibit the esterification of other fatty acids.[1] Further, *in vitro* studies have confirmed that application of EPA to hepatocyte cell cultures inhibit TG synthesis and stimulate membrane phospholipid synthesis.

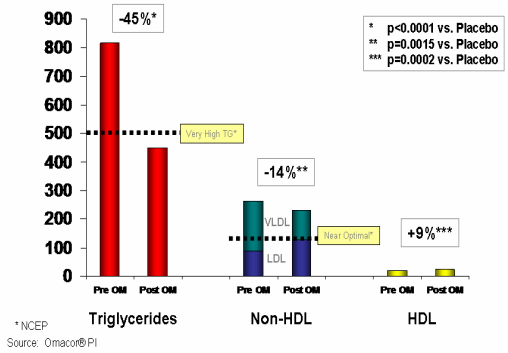
Increases in the TG content of VLDL or remnant particles have been shown to increase the activity of CETP that result in the generation of atherogenic sdLDL-C particles[34] with Lovaza™ reduces CETP activity in hypertriglyceridemic patients and shifts the LDL-C subfraction from a predominance of small and dense pattern to a distribution with large and more buoyant particles. [62]

In a pooled study (Table 2.5 and Figure 2.11) of patients with TG levels ≥500 mg/dL, treatment with 4 g/d of Lovaza™ for 6 or 16 weeks resulted in significant reductions in median TG (-44.9%), TC (-9.7%), VLDL-C (-41.7%) and non–HDL-C (-13.8%) levels, whereas HDL-C was raised by 9.1% relative to placebo.[1] It is important to note that the LDL-C levels at baseline were low in this population (89 mg/dL for the Lovaza™ group) and that a significant decrease of 13.8% was observed in the atherogenic non–HDL-C pool, which includes VLDL-C and LDL-C.[1]

Table 2.5 Pooled Analysis of Patients with TG ≥500 mg/dL[1]

Lipid Parameter (mg/dL)	Treatment Group	Baseline	% Change
TG	Placebo Lovaza™	788 816	6.7 -44.9
LDL-C	Placebo Lovaza™	108 89	-4.8 44.5
TC	Placebo Lovaza™	314 296	-1.7 -9.7
HDL-C	Placebo Lovaza™	24 22	0 9.1
VLDL-C	Placebo Lovaza™	175 175	-0.9 -41.7
Non-HDL-C	Placebo Lovaza™	292 271	-3.6 -13.8

Figure 2.11 Pooled Analysis of Patients with TG ≥500 mg/dL[1]



Several studies have demonstrated that Lovaza™ 4 g/d can be safely combined with a statin therapy. In a randomized, double-blind, placebo-controlled study, patients with persistent hypertriglyceridemia (200-499 mg/dL) who received 8 weeks of open-label simvastatin (40 mg/d) were randomized to 8 weeks of

double-blind treatment with either Lovaza™ 4 g/d plus simvastatin 40 mg/d or placebo plus simvastatin 40 mg/d.[63] The combination of Lovaza™ plus simvastatin significantly reduced non–HDL-C (-9% vs. -2.2%, *P* <.001) and TG levels (-29.5% vs -6.3%, *P* <.001), and increased HDL-C (3.4% vs -1.2%, *P* <.001), relative to placebo. Authors concluded that the combination of Lovaza™ and simvastatin improved the overall lipid profile without attenuating the efficacy of the statin.

In a 48-week randomized, placebo-controlled study, Durrington et al examined the safety and efficacy of Lovaza™ 4 g/d versus placebo (corn oil) among patients with TG ≥200 mg/dL who were already receiving a stable dose of simvastatin 10-40 mg/d.[64]Treatment with Lovaza™ plus simvastatin resulted in additional 20% to 30% reduction in TG levels compared with simvastatin alone. Investigators concluded that Lovaza™ is a safe and effective means of lowering TG levels in patients with CHD and combined hyperlipidemia whose TG levels remain elevated despite statin monotherapy.

Chan et al[65] conducted a 6-week, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of atorvastatin (40 mg/d) and Lovaza™ (4 g/d) in patients with insulin-resistance. Treatment with atorvastatin plus Lovaza™ significantly reduced TG levels compared with atorvastatin alone (-40% vs -23%, respectively), and raised HDL-C levels (13.6% vs 4%, respectively). There were no significant changes in insulin sensitivity or body weight. Authors concluded that atorvastatin in combination with Lovaza™ was an effective method of therapy for obese subjects with insulin resistance and dyslipidemia compared with either treatment alone.

At therapeutic doses of Lovaza™, clinically significant drug-drug interactions due to inhibition of cytochrome P450 dependent activities are not expected.[1] Omega-3 fatty acids may have antithrombotic effects. However, to date, no published studies have demonstrated significant changes in bleeding time or propensity for bleeding among patients treated with FDA-approved doses of Lovaza™.[21, 22] A study on the interaction between fish oil and warfarin did not show increases in major bleeding episodes, or the dosage of warfarin was not reduced. Moreover, omega-3 fatty acid therapy in patients receiving aspirin or other antiplatelet agents has not been associated with an increase in bleeding.[22-24] A recent review of the literature on the risk of bleeding associated with omega-3 fatty acids concluded that the risk of clinically significant bleeding was virtually nonexistent.[22] Nevertheless, the FDA does mandate that patients should take large doses of omega-3 fatty acids only under physician supervision. Although additional blood testing is not required for patients taking approved doses of Lovaza™, patients should be monitored for signs and symptoms of bleeding prior to, and throughout, treatment with Lovaza™.[1]

Fibric Acid Derivatives

Fibric acid derivatives include fibrates (such as gemfibrozil/LOPID®) and fenofibrates (such as Antara® and TriCor®). The mechanism of action of fibric acid derivatives remains unclear. Treatment with fibric acid derivatives may increase TG clearance and decrease hepatic TG synthesis.[32]

Among patients with TG <500 mg/dL, treatment with fibrates and fenofibrates decreased TG levels by 50%, increased HDL-C approximately 15%, and decreased LDL-C by 15% to 20%. Among patients with TG ≥500 mg/dL, fibrates and fenofibrates were shown to decrease TG levels by 50% and increase HDL-C levels by 15%. However, LDL-C levels increased by 10% to 30% in patients with high TG.[32] Westphal et al noted that because absolute LDL-C levels are generally low among patients with very high TG, a modest increase in LDL-C levels is not a cause for clinical concern.[66]

Mild side effects may occur in 5% to 10% of patients, and include gastrointestinal disorders, rash, urticaria, myalgias, fatigue, headache, and anemia.[25, 26] Minor increases in liver transaminases and decrease in alkaline phosphatase may occur. Because fibric acid derivatives may potentiate the action of oral anticoagulants, careful monitoring of prothrombin time and reduction in anticoagulant dose is appropriate

A myositis flu-like syndrome occasionally occurs in patients treated with fibric acid derivatives.[67] The

clinical presentation varies, but typically includes muscle pain, weakness, and tenderness, and moderate to markedly elevated serum creatinine kinase activity; rapid remission of symptoms after discontinuation of therapy usually occurs. In a population-based cohort study to estimate the risk of drug related myopathy, Gaist and associates found that the absolute 1-year risk of myopathy among patients treated with fibrates was 6 in 10,000 individuals. The relative risk of myopathy among current users of fibrates compared with non-users was 42.4 (95% CI = 11.6 –170.5). Authors concluded that there was a marked increase in the relative risk for myopathy with fibrates; however the absolute risk of myopathy was small.

Use of combined lipid-lowering drugs with statins may increase the risk of myopathy and result in a more severe clinical presentation, occasionally leading to rhabdomyolysis.[32] Use of fibrates with cerivastatin should be avoided because of the potential for this disorder.[25, 26] The pathogenesis underlying drug-induced rhabdomyolysis is currently unknown. [67] Hepatic dysfunction and renal failure are relative contraindications that are associated with the use of fibric acid derivatives. [25, 26] Fibrates should not be used by children or pregnant women.

Nicotinic acid

Niacin (used synonymously with nicotinic acid) is a water-soluble B-complex vitamin that is converted to nicotinamide adenine dinucleotide.[32] The effect of nicotinic acid may be mediated in part by a decrease in the release of free fatty acids from adipose tissue, thereby decreasing the influx of free fatty acids to the liver, reduction in the hepatic re-esterification of free fatty acids and in the rate of production of hepatic VLDL.[68] A decrease in the hepatic VLDL-C reduces the level of circulating VLDL available for conversion to LDL-C. Nicotinic acid may also act by directly inhibiting hepatic synthesis or secretion of apo B-containing lipoproteins.[69] Finally, nicotinic acid may elevate HDL-C levels primarily by suppressing the hepatic removal of apo A-1, which increases levels of apo A-I as well as large apo A-I containing HDL-C particles.

Treatment with niacin resulted in significant reductions in the levels of TG (35 - 40%), LDL-C (20-30%), and $Lp_{(a)}$ (40%), whereas HDL-C levels were raised by 30% to 40%.[32] However, vasodilation-related side effects—flushing, itching, and headache—as well as dyspepsia, frequently limit patient compliance with niacin; about 30% of patients experience side effects that result in discontinuation of therapy.[32]

The most common serious side effects associated with niacin are hepatotoxicity and hyperglycemia.[32] The sustained-release formulation may be less likely to cause severe hepatotoxicity, although several cases of hepatic failure have been documented.[32] Combination of statin + low-dose niacin can be used effectively in patients with low HDL-C and elevated TG levels; however, myopathy may occur in response to liver toxicity and impaired hepatic statin metabolism. In patients with diabetes mellitus, niacin-induced insulin resistance can cause hyperglycemia.[32] Consequently, niacin is not recommended for use in these patients. In addition, niacin should not be used in patients with a history of gout because the drug elevates uric acid.[32]

2.6 FDA Position on Dietary Supplements for the Treatment of Hypertriglyceridemia

Dietary supplements defined

Unlike prescription drugs, there is no burden of proof for efficacy, safety, or purity placed upon manufacturers of supplements. Supplement manufacturers do not have to provide the FDA with evidence that dietary supplements are effective or safe. However, they are not permitted to market unsafe or ineffective products. Once a dietary supplement is marketed, the FDA has to prove that the product is not safe in order to restrict its use or remove it from the market.[70]

Not a therapeutic option for the treatment of disease

The FDA has deemed that dietary supplements are not permitted to claim to diagnose, cure, mitigate, treat, or prevent disease.[70] The FDA does not evaluate efficacy or safety data of omega-3 dietary

supplements and thus does not approve omega-3 dietary supplements for the treatment of a disease but restricts dietary supplements to a qualified health claim. A qualified health claim supports the supplementation of essential nutritional products in order to maintain good health.[71, 72] In 2004, the FDA approved a qualified health claim for omega-3 fatty acids, which allows foods and supplements containing EPA and DHA omega-3 fatty acids to claim that "supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease." [70, 73]The FDA determined that dietary supplements should not recommend or suggest in their labeling a daily intake exceeding 2 g of EPA and DHA to ensure that individuals do not exceed the maximum daily dose of 3 g per person per day from conventional foods and dietary supplement sources. At therapeutic levels of 3.6 g omega-3 fatty acids, the FDA does not provide an option for the treatment of hypertriglyceridemia with dietary supplements.

Dietary supplements as a treatment option by-pass the physician and pharmacist's ability to manage the patient's disease in the context of other medications. The FDA and the American Heart Association both support the management of hypertriglyceridemia under the supervision of a physician. An important benefit of physician supervision is to ensure that patients receive appropriate monitoring for safe treatment. Although clinical trials have shown high-dose fish oil omega-3 fatty acid consumption to be safe, even when concurrently administered with other agents that may increase bleeding (e.g., aspirin, warfarin),[22] because of the theoretical risk, the FDA mandates that patients be given large doses of omega-3 fatty acids only under physician supervision. [74]

Compliance with supplements

Beyond safety, concentration, and lack of FDA support, the daily number of dietary capsules required to achieve equivalent doses to Lovaza™ (3.6 g/d of EPA/DHA, not necessarily therapeutic equivalent) raises the issue of compliance, especially outside of the physician's awareness. In earlier clinical trials 15-18 capsules daily of dietary-supplement of omega-3 fatty acids were required in an effort to achieve a dose of EPA plus DHA that approximated that of Lovaza™ [75]

2.7 Fish Intake for the Treatment of Hypertriglyceridemia

Fish Intake: estimates from the USDA Nutrient Data Laboratory on the amount of daily fish consumption required to achieve therapeutic levels of EPA and DHA are shown in Table 2.6.[74] Results suggest that the amount of fish consumption required to achieve the therapeutic dose of 4 g of EPA and DHA per day for treatment of TG $\geq$500 mg/dL is extreme. The daily consumption of large quantities of fish is not feasible, and introduces safety concerns regarding exposure to environmental pollutants, in particular PCB and methylmercury.[59]

Due to the high quantity of daily fish consumption required to achieve therapeutic levels of omega-3 fatty acids, the American Heart Association's Scientific Statement acknowledges that capsules are the only way to consistently achieve doses of omega-3 fatty acids greater than 3 g per day.[76]

Table 2.6 Estimated Daily Requirements of Fish Consumption Required to Achieve Therapeutic Levels of EPA and DHA[74]

FISH		EPA + DHA Content, g/3-oz serving fish (Edible Portion)	Ounces of fish required to provide ~ 4g of EPA + DHA per day	Number of 3-oz servings required per day to provide ~4g EPA + DHA
Tuna				
	Light canned in water, drained	0.26	48 oz	16 servings
	White, canned in water, drained	0.73	16 oz	5 servings
	Fresh	0.24 - 1.28	10 to 48 oz	3 to 16 servings
Sardines		0.98-1.70	8 to 12 oz	3 to 4 servings
Salmon	Chum	0.68	18 oz	6 servings
	Sockeye	0.68	18 oz	6 servings
	Pink	1.09	10 oz	3 servings
	Chinook	1.48	8 oz	3 servings
	Atlantic, farmed	1.09-1.83	6 to 10 oz	2 to 3 servings
	Atlantic, wild	0.9-1.56	8 to 14 oz	3 to 5 servings
Macarel		0.34-1.57	8 to 34 oz	3 to 11 servings
Herring	Pacific	1.81	6 oz	2 servings
	Atlantic	1.71	8 oz	3 servings
Trout, rainbow	Farmed	0.98	12 oz	4 servings
	Wild	0.84	14 oz	5 servings
Halibut		0.4-1.0	12 to 30 oz	4 to 10 servings
Cod	Pacific	0.13	92 oz	31 servings
	Atlantic	0.24	50 oz	17 servings
Haddock		0.2	60 oz	20 servings
Catfish	Farmed	0.15	80 oz	27 servings
	Wild	0.2	60 oz	20 servings
Flounder/Sole		0.42	28 oz	9 servings
Oyster	Pacific	1.17	10 oz	3 servings
	Eastern	0.47	26 oz	9 servings
	farmed	0.37	32 oz	11 servings
Lobster		0.07-0.41	30 to 170 oz	10 to 57 servings
Crab, Alaskan King		0.35	34 oz	11 servings
Shrimp, mixed species		0.27	44 oz	15 servings
Clam		0.24	50 oz	17 servings
Scallop		0.17	70 oz	23 servings

2.8. Expected Outcomes of Therapy

Among patients with very high TG levels (≥500 mg/dL), Lovaza™ monotherapy (4 g per day) reduced TG levels by 51.6% and increased HDL-C by 9.1% compared with placebo.[1] Lovaza™ administered concomitantly with a statin further reduced TG levels by 20-30% and raised HDL-C levels by 2% to 5%, compared with statin treatment alone.[64]

The effects of Lovaza™ monotherapy and in combination with statins are summarized below:

Lovaza™ Monotherapy in Patients with TG ≥500 mg/day

- Harris et al conducted a randomized double-blind, parallel-group, study in which 43 hypertriglyceridemic patients (TG 500-2000 mg/dL) were treated with Lovaza™ 4 g/d and placebo for 16 weeks. Treatment with Lovaza™ resulted in reductions in serum TG and VLDL-C levels from baseline -45%; *P* < .0001 and -43.4%; *P* = .0001, respectively. Serum HDL-C and LDL-C levels increased by 13.3% (*P* = .014) and 31.6% (*P* = .0014) from baseline, respectively. Lovaza™ was well tolerated and 1 patient discontinued therapy because of adverse effects. [77]

- Pownall et al conducted a randomized, double-blind parallel-group trial in which 40 patients with

severe type IV hypertriglyceridemia (TG 500-2000 mg/dL) received either Lovaza™ 4 g/d or placebo for 6 weeks. The studies included 6 weeks of dietary lead in and 6 weeks of double-blind intervention. Eight of the patients were type-2 diabetics. Treatment with Lovaza™ resulted in reductions in serum TG and VLDL-C from baseline (-38.9%, *P* = .001 and 29.2%, *P* = .001, respectively). Serum HDL-C concentrations rose by 5.9% from baseline (*P* = .057) while LDL-C increased by 16.7% from baseline. The changes noted above were significantly different from placebo [78]

Safety and Efficacy of Lovaza™ Combination Therapy with Statins

- Davidson et al conducted a multicenter, randomized, double-blind, placebo-controlled study in patients with persistent hypertriglyceridemia (TG 200-499 mg/dL) while on stable simvastatin therapy (n = 254). The addition of Lovaza™ (4 g/d) to simvastatin (40 mg/d) therapy for 8 weeks resulted in a median percent decrease in non–HDL-C that was significantly greater than observed in the group receiving placebo plus simvastatin (9.0% vs 2.2%, respectively; *P* <.0001). Combination therapy significantly lowered TG (29.5% vs 6.3%) and VLDL-C (27.5% vs 7.2%), raised HDL-C (+3.4% vs –1.2%), and lowered TC:HDL-C ratio (9.6% vs 0.7%; *P* < .0001 vs placebo for all).[79]

- McKenney et al conducted an open-label, randomized, 2-way crossover, drug-drug interaction study on healthy volunteers (n = 24) and found that concomitant treatment with simvastatin (80 mg/day) and Lovaza™ (4 g/day) for 2 weeks did not result in statistically significant changes in the pharmacokinetic parameters of simvastatin compared with treatment with simvastatin alone. [80]

- Chan et al conducted a randomized placebo-controlled, double-blind study to evaluate the independent and combined effects of atorvastatin and Lovaza™ in insulin-resistant obese male patients (n = 48). Atorvastatin alone significantly decreased plasma levels of TG, TC, non–HDL-C , LDL-C, and apo B and increased HDL-C (*P* < .01). There was also a significant main effect of Lovaza™ in lowering plasma TG and raising HDL-C. No significant interactions between atorvastatin and Lovaza™ treatment were found for any of the measured variables. [81]

- Durrington et al conducted a double-blind, placebo-controlled study in which hyperlipidemic patients (n = 59) with coronary heart disease on stable simvastatin therapy (10 to 40 mg/d) received Lovaza™ (4 g/d) or placebo for 48 weeks.[82] The addition of Lovaza™ resulted in significant reductions in plasma TG (-23.9%) and VLDL-C (-40%) levels in patients on stable simvastatin therapy.[64]

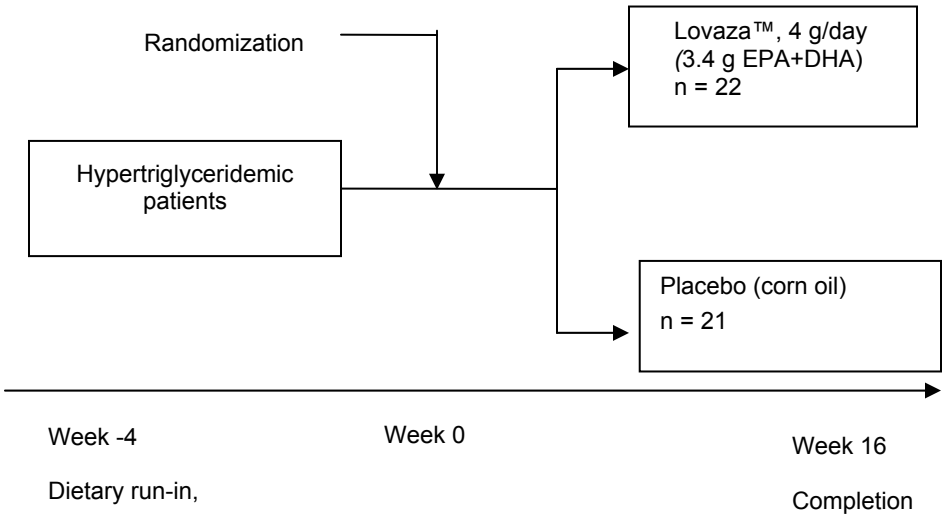
3.0 SUPPORTING CLINICAL INFORMATION

3.1 Pivotal Safety and Efficacy Studies: Lovaza™ 4 g/d Monotherapy for Treatment of Very High Hypertriglyceridemia (TG ≥500mg/dL)

3.11 Harris WS, Ginsberg HN, Arunakul N, Shachter NS, Windson SL, Adams M, Berglund L, Osmundsen K. Safety and efficacy of Omacor in severe Hypertrigyceridemia. *J Cardiovasc Risk.* 1997;4:385-391.[77]

Study Design: Harris et al conducted a randomized, double-blind, parallel-group study where hypertriglyceridemic patients received Lovaza™ 4 g/day for 16 weeks. The data from this study was used in the submission package to the FDA for the use of Lovaza™ to reduce very high (≥500 mg/dL or 5.6 mmol/L) TG levels in adult patients. Study design is shown in Figure 1

Figure 1. Study Design



Serum TGs were measured 4 times 1 week apart (-4, -2, -1, and 0) during the run-in phase. The mean of weeks -2, -1, and 0 for baseline values was used in subsequent data analysis. Endpoint values were defined as the mean of 2 measurements 2 weeks apart (treatment weeks 14 and 16).

Inclusion Criteria: Patients aged between 18 and 75 years with serum TG >500 mg/dL (5.6 mmol/L) and < 2000 mg/dL (22.5 mmol/L).

Exclusion Criteria: Patients with TG concentrations exceeding 2000 mg/dL, (22.5 mmol/L); patients who consumed cold-water fish more than once weekly; those with type III hyperlipidemia, myocardial infarction less than 6 months before entering the study. Serum alanine aminotransferase more than 3 times the upper normal value, fasting serum glucose >200 mg/dL, (11.1 mmol/L), serum creatinine >2 mg/dl, platelet counts <60 × 10^9/L, hemoglobin <10 g/dL, or the presence of any clinically significant disease (as judged by the investigators). Female patients were not accepted if they were pregnant or breastfeeding. Excessive use of alcohol (more than 2 drinks per day), drug abuse, or any conditions associated with risk of poor compliance were also grounds for exclusion. More than 6 weeks of washout of ongoing fibrate therapy was required prior to the 4-week dietary run-in phase. Additionally, patients were not allowed to receive lipid-decreasing fibers, cod liver oil, or other products containing omega-3 fatty acids within 4 weeks of beginning the study.

Baseline characteristics were similar between the 2 groups.

Outcome measures: Changes in TG concentrations from baseline to end of study. Secondary endpoints included changes from baseline in TC, VLDL-C, HDL-C, LDL-C, and apolipoprotein A-1 (Apo-A1).

Results: All patients who successfully completed the trial were included in the final analysis. One patient was withdrawn from the study after 1 month of placebo treatment because his private physician suggested that he discontinue the study drug and start statin therapy. The final data set included 22 patients in the Lovaza™ group and 20 in the placebo group. Overall compliance averaged 94% (range 66%-100%) with no differences noted between groups.

The median percent changes in lipid parameters are presented in Table 1.Treatment with Lovaza™ resulted in significant reductions from baseline in serum TG (-45%; *P* < .0001) and VLDL-C (-43.4%; *P* =.0001). HDL-C levels increased from baseline (13.3%; *P* = .014) in patients receiving Lovaza™ while LDL-C levels increased by 31.6% (*P* = .0014).

Table 1. Effects of Intervention on Median Lipid Concentrations after 4 Months of Treatment

	Placebo		Lovaza™		*P* Value
	Baseline	Endpoint	Baseline	Endpoint	
TC					
mg/dL	301 ± 82	295 ± 79	268 ± 70	228 ± 50	.033
mmol/L*	7.7 ± 2.1	7.6 ± 2.0	6.9 ± 1.8	5.8 ± 1.3	
TG					
mg/dL	877 ± 271	1007 ± 408	919 ± 381	505 ± 304	<.0001
mmol/L*	9.9 ± 3.0	11.3 ± 4.6	10.3 ± 4.3	5.7 ± 3.4	
VLDL-C					
mg/dL	177 ± 88	76 ± 92	159 ± 86	90 ± 49	.001
mmol/L*	4.5 ± 2.3	1.9 ± 2.4	4.1 ± 2.2	2.3 ± 1.3	
LDL-C					
mg/dL	96 ± 36	91 ± 35	79 ± 36	104 ± 38	.002
mmol/L*	2.5 ± 0.9	2.3 ± 0.9	2.0 ± 0.9	2.7 ± 1.0	
HDL-C					.004
mg/dL	28 ± 7	28 ± 8	30 ± 13	34 ±14	
mmol/L*	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.3	0.9 ± 0.4	
Cholesterol/HDL	3.4 ± 1.1	3.2 ± 0.9	2.9 ± 1.3	3.3 ± 1.4	NS
Apo A-I (g/L)	1.28 ± 0.26	1.26 ± 0.27	1.32 ± 0.41	1.31 ± 0.34	NS

*Data presented in mg/dL was converted to mmol/L: conversion factors—TG⁄89, TC⁄39, HDL-C, LDL-C, VLDL-C:⁄39.

Safety: Gastrointestinal side effects occurred in 4 patients in the Lovaza™ group and in 3 patients who received placebo. None of the treatment-related side effects were serious, and side effects did not lead to discontinuation of treatment in any of the patients. Lovaza had no significant effect on any laboratory parameters including glucose, hemoglobin A_{1c}, liver enzymes, kidney function, or platelet counts.

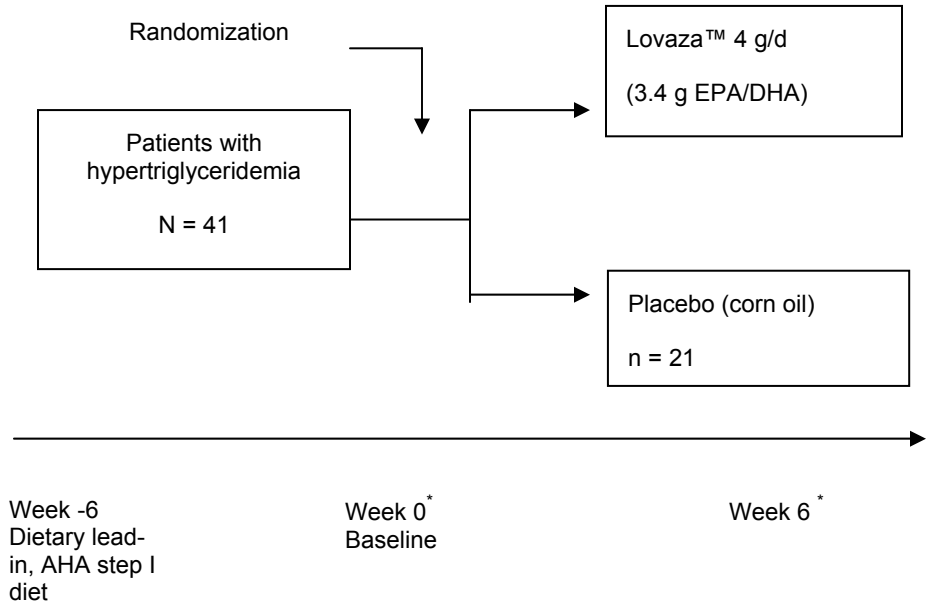
Conclusion: The study concluded that treatment with Lovaza™ significantly decreased the levels of TG in patients with severe hypertriglyceridemia. The authors noted that treatment with Lovaza™ may reduce the risk of developing acute pancreatitis and diminish the long-term risk of cardiovascular disease in patients with hypertriglyceridemia.

3.12 Pownall HJ, Brauchi D, Kilinc C, Osmundsen K, Pao Q, Payton-Ross C, Gotto Jr AM, Ballantyne CM. Correlation of serum triglyceride and its reduction by omega-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins. *Atherosclerosis* 1999;143:285-297.[78]

Study Design: Pownall et al conducted a randomized, double-blind, parallel-group trial in which hypertriglyceridemic patients received Lovaza™ 4 g/d and placebo for 6 weeks.

The data from this study was used in the submission package to the FDA for the use of Lovaza™ to reduce very high (≥500 mg/dL or 5.6 mmol/L) TG levels in adult patients. Study design is shown in Figure 1.

Figure 1. Study Design.



*Clinic visits were scheduled for mornings after minimum of 12 h fasting and 24 h abstention from alcohol. The baseline serum TG value for the assessment of efficacy was defined as the median of fasting values from weeks -2, -1 and 0. The serum TG value with treatment was defined as the median of fasting values from weeks 4, 5 and 6.

Inclusion Criteria: Men and women aged 18 to 70 years with mean serum (TG ≥500 mg/dL or 5.6 mmol/L) but ≤2000 mg/dL (22.5 mmol/L) despite dietary counseling.

Exclusion criteria: Treatment with a fibrate <3 months before entering the dietary phase. Treatment with another omega-3 fatty acid product, cod-liver oil, or a dietary fiber with lipid-lowering effects < 4 weeks before entering the dietary phase. Consumption of cold-water fish more than once a week. Myocardial infarction or another serious disease <6 months before baseline. Serum alanine transaminase >3 times the upper limit of normal; fasting serum glucose >300 mg/dL (16.7 mmol/L); serum creatinine >176.8 µmol/L; platelets <60 × 10^9/L; hemoglobin <100 g/L. Pregnancy or breast-feeding; alcohol or drug abuse; and type1 diabetes mellitus.

Eight patients had prior diagnosis of type 2 diabetes; 4 were treated with insulin, 2 with oral agents, and 2 with lifestyle modifications.

Outcome measures: Change in serum concentrations of TG.

No significant differences in baseline age, height, or body-weight was noted between the 2 groups.

Results: One subject randomized to receive Lovaza™ did not complete the study and was excluded from data analysis.

The median percent changes from baseline in lipid parameters are presented in Table 1 and Figure 2. Treatment with Lovaza™ resulted in reduction from baseline in serum TG (-38.9%; *P* = .001) and VLDL-C (-29.2%; *P* = .001). Serum HDL-C increased by 5.9% (*P* = .057) from baseline in the Lovaza™ group (*P* =

.023 compared with the placebo group). Serum LDL-C increased by 16.7% from baseline (43 to 53 mg/dL; *P* = .007) in the Lovaza™ group.

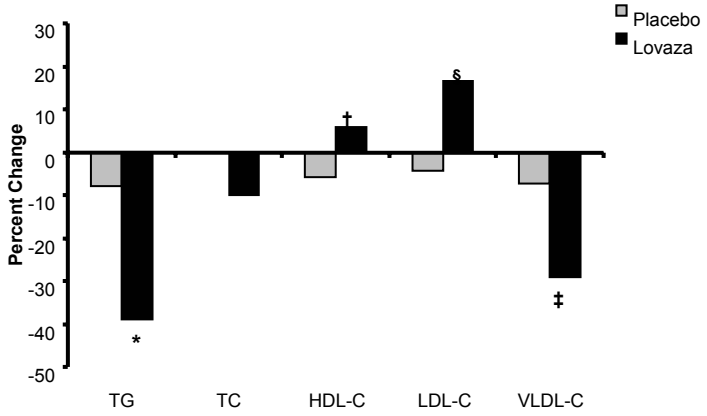
Table 1. Effects of Intervention on Median Lipid Concentrations

	Placebo (n = 21)				Lovaza™ (n = 19)				
Analyses	Baseline	Endpoint	% Change	*P* Value[b]	Baseline	Endpoint	% Change	*P* Value[b]	Between Group *P*[c]
TG									
mg/dL	786	664	-7.8	NS	801	512	-38.9	.001	.001
mmol/L[a]	8.8	7.5			9.0	5.6			
TC									
mg/dL	328	328	0	NS	326	288	-9.9	.004	099
mmol/L[a]	8.4	8.4			8.4	7.4			
HDL-C									
mg/dL	18	16	-5.9	NS	17	18	+5.9	.057	.023
mmol/L[a]	0.5	0.4			0.4	0.5			
LDL-C									
mg/dL	60	57	-4.2	NS	43	53	+16.7	.007	.013
mmol/L[a]	1.5	1.5			1.1	1.4			
VLDL-C									
mg/dL	179	177	-7.3	NS	185	136	-29.2	.001	.002
mmol/L[a]	4.6	4.5			4.7	3.5			

[a]Data presented in mg/dL were converted to mmol/L: conversion factors—(TG⁄89), (TC⁄39), (HDL-C, LDL-C, VLDL-C⁄39).

[b]Wilcoxon signed rank test was used to compare medians.; [c]Mann-Whitney analysis was used to compare medians.

Figure 2. Median Percent Change From Baseline in Lipid Parameters Following Treatment with Lovaza™ or Placebo for 6 Weeks



* *P* = .001; † *P* = .023; ‡ *P* = .002; § *P* = .013 (all vs placebo)

For further information regarding other aspects of this study see publication.

Safety: There were no serious side effects reported. Lovaza™ did not adversely affect blood pressure, alanine transaminase values, or aspartate transaminase values, and glucose concentrations remained within enrollment criteria (actual values were not reported).

Conclusion: The primary clinical objective of the study was to determine the effects of Lovaza™ on serum lipid variables. Treatment with Lovaza™ significantly lowered serum TG, TC and VLDL-C and increased HDL-C and LDL-C levels from baseline in patients with hypertriglyceridemia.

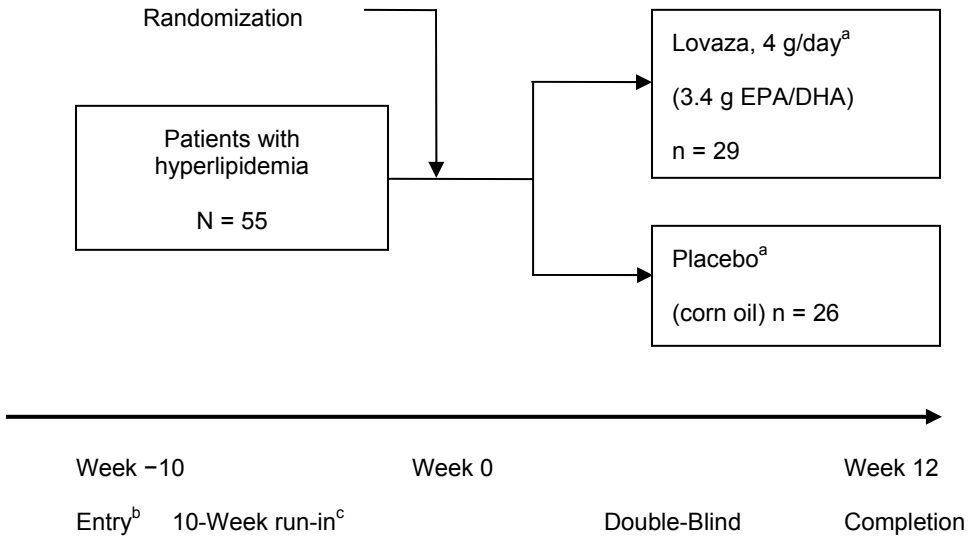
3.2 Safety and Efficacy Studies: Lovaza™ 4 g/d Monotherapy for Treatment of high and Very High Hypertriglyceridemia (TG >200 mg/dL)

3.21 Borthwick L. The effects of an omega-3 ethyl ester concentrate on blood lipid concentrations in patients with hyperlipidaemia. *Clin Pharmacodynamics* 1998;15:397-404.[82]

Study Design

Borthwick et al conducted a randomized, double-blind, placebo-controlled, multicenter study to assess the effects and tolerability of Lovaza™ monotherapy in patients with hyperlipidemia. The study was sponsored by Pronova Biocare, Norway. Study design is shown in Figure 1.

Figure 1



[a]Patients received 2 g twice daily
[b]Eighty-four patients were enrolled.
[c]After the 10-week dietary run-in, 55 patients who met the inclusion criteria were randomized for the intervention phase.

Inclusion criteria: Patients, aged 18 to 70 years, who were newly diagnosed with hyperlipidemia, as well as those with pre-existing hyperlipidemia who were receiving either dietary therapy or medication that could be withdrawn for the duration of the study were included. For inclusion in the intervention phase, mean fasting TG levels between 178 mg/dL (2 mmol/L) and 890 mg/dL (10 mmol/L), and TC ≥ 203 mg/dL (5.2 mmol/L) were required. A change in body weight during the run-in period of less than 1 kg/week was also required.

Exclusion criteria: not stated in the study.

Tests performed**:** Serum TG, TC, and HDL-C levels were measured at weeks −8, −6, 0, 14, 18, and 22.

Outcome measures: Changes in serum lipid parameters and EPA/DHA levels in patients with hyperlipidemia.

Baseline clinical characteristics were similar among patients in the 2 treatment groups

Results: Forty-seven patients completed the study. Eight patients in total (5 from Lovaza™ and 3 from placebo) withdrew from the study for reasons of adverse events, poor compliance, or violation of protocol.

Treatment with Lovaza™ resulted in reductions in plasma TG levels from baseline to end of treatment, compared with a non-significant increase in the placebo group (Table 1). No significant changes were found in other lipid parameters between or within treatment groups. After 12 weeks of treatment with Lovaza™ a significant increase in the EPA/DHA content of serum phospholipids was noted, compared with placebo ($P < .0001$

Table 1. Change in Serum TG Levels after Treatment with Lovaza™ or Placebo.

	Mean percent change from baseline to end of treatment (12 w)	
	Lovaza™	Placebo
Serum TG	−28.3 ± 19.1[a,b]	9.1 ± 24.8

Data are presented as mean ± SD.
[a] P =.0001 for significance of change within group.
[b] $P < .0001$ for significance of change between treatment groups.

Safety: Thirty-two adverse events were reported by 20 of 29 (69%) patients who received Lovaza™ treatment: 13 events were considered related to the treatment. In the placebo group, 12 of 26 (46%) patients reported 20 adverse events, of which 5 were considered related to the treatment. Gastrointestinal effects including nausea, indigestion, and diarrhea were the most prevalent adverse effects, while influenza, sore throat, rash, chest infection, and headache were also reported. Four of the 5 adverse events, classified as severe, occurred in the Lovaza™ group and included nausea (2), nonspecific backache (1), and suspected unstable angina (1).

Four patients experienced 5 serious adverse events during the trial. Two of the events—unstable angina and collapse due to a brainstem cerebrovascular accident— occurred during the run-in phase. The other serious events—unstable angina and increasing angina—occurred in 2 patients (one from each group) during the intervention phase.

Conclusion: The study concluded that administration of Lovaza™ 4 g/d to patients with hyperlipidemia

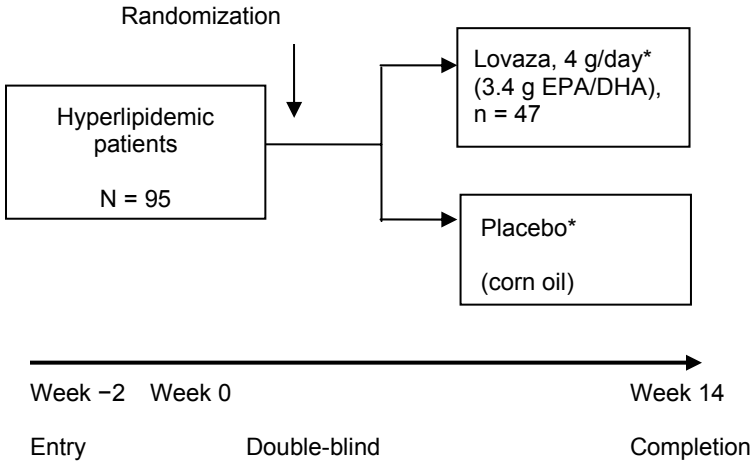
was sufficient to achieve a substantial TG-lowering effect (-28%) compared with a non-significant increase in the placebo group.

3.22 Mackness MI, Bhatnagar D, Durrington PN, Prais H, Haynes B, Morgan J, Borthwidk L. Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridaemia. *Eur J Clin Nutr.* 1994; 48:859-865.[83]

Study Design

Mackness et al conducted a randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy of Lovaza™ monotherapy in patients with hyperlipidemia. The study was supported by Pronova Biocare, Oslo, Norway. Study design is shown in Figure 1.

Figure 1



*Patients received 2 g twice daily.

Inclusion criteria: Patients, aged 18 to 70 years, with primary type IIb or type IV hyperlipidemia: fasting serum TG levels between 178 mg/dL (2 mmol/L) and 890 mg/dL (10 mmol/L) and total cholesterol >203 mg/dL (5.2 mmol/L).

Exclusion criteria: Patients with diabetes mellitus, hypothyroidism, serious illness in the previous 3 months, including myocardial infarction, or severe concurrent illness were excluded, as were drug or alcohol abusers, and pregnant or lactating women.

Tests performed: Fasting levels of serum TG, TC, VLDL-C, LDL-C, HDL-C, and Lp(a) were assessed at weeks −2, 0, 6, 10, and 14 of the study. In addition, blood pressure and fasting glucose levels were measured.

Outcome measures: Changes in serum concentrations of lipids and lipoproteins. Patient characteristics at baseline were similar between groups.

Results: Ninety-five patients entered the study and 79 completed the study (41 patients from the Lovaza™ group and 38 from the placebo group). Sixteen subjects in total (6 from the Lovaza™ group and 10 from the placebo group) were withdrawn from the study because of adverse events (8), non-compliance (2), or personal reasons (6). Levels of serum TG and VLDL-C were significantly reduced from baseline after 14 weeks of treatment with Lovaza™(Table 1);however, the concentrations of serum TC, LDL-C, HDL-C, or Lp(a) did not change significantly. No significant changes from baseline were observed in lipid parameters of patients receiving placebo.

Table 1. Lipid Parameters Measured at Baseline and at Week 14 after Treatment with Lovaza™

	Baseline	Week 14	Change from Baseline	Change from Placebo
Serum TG				
mmol/L	3.99 (2.94-9.47)	2.87 (1.2-9.93)	*P* < .001	*P* < .01
mg/dL[b]	355 (262-42)	255 (107-884)		
VLDL-C				
mmol/L	1.47 (0.77-3.63)	1.12 (0.21-3.67)	*P* < .001	*P* < .01
mg/dL[b]	57 (30-1420)	44 (8.2-143)		

[a]Values are presented as median (range).
[b]Data reported in mmol/L were converted to mg/dL: conversion factors—TG (×89) and VLDL-C (×39).

In a secondary analysis, patients were divided into 2 groups according to their LDL-C levels; patients with LDL-C levels >176 mg/dL (>4.5 mmol/L, Type IIb hyperlipidemia) and those with LDL-C levels <176 mg/dL (<4.5 mmol/L, Type IV hyperlipidemia). After 14 weeks of treatment with Lovaza™, serum TG and VLDL-C levels were reduced significantly from baseline in patients with Type IIb hyperlipidemia (Table 2).

Table 2. Effect of Lovaza™ in Patients with Type IV Hyperlipidemia and Type IIb Hyperlipidemia

	Type IV (n = 18)		Type IIb (n = 23)	
	Week 0	Week 14	Week 0	Week 14
TG[a]				
mmol/L	4.59 (2.35-9.47)	3.61 (1.2-8.93)*	3.7(2.24-6.52)	2.44(1.58-3.43)***
mg/dL[b]	408 (209-843)	322 (107-795)*	329 (199-580)	217 (141-305)***
TC				
mmol/L	7.16 ± 1.49	7.41 ± 1.73	8.49 ± 0.74	8.09 ± 1.24
mg/dL[b]	279 ± 58	289 ± 68	331 ± 29	315 ± 48
VLDL-C[a]				
mmol/L	1.87(0.94-3.63)	1.37(0.21-3.67)**	1.52(0.77-2.62)	1.01(0.59-1.87)***
mg/dL[b]	73 (37-142)	53 (8-143)**	59 (30-102)	39 (23-73)***
HDL-C				
mmol/L	0.98 ± 0.25	1.11 ± 0.33**	0.98 ± 0.18	1.05 ± 0.27
mg/dL[b]	38 ± 10	43 ± 13**	38 ± 7	41 ± 11
LDL-C				
mmol/L	3.6 ± 0.66	3.93 ± 1.12	5.63 ± 0.69	5.53 ± 1.33
mg/dL[b]	140 ± 26	153 ± 44	220 ± 27	216 ± 52

Values are presented as mean ± SD except when indicated[a], which are median and range.
[b]Data reported in mmol/L were converted to mg/dL: conversion factors—TG (×89), TC (×39), lipoproteins (×39).
Significantly different from value at week 0: *P < .05, **P < .01,**P < .001.

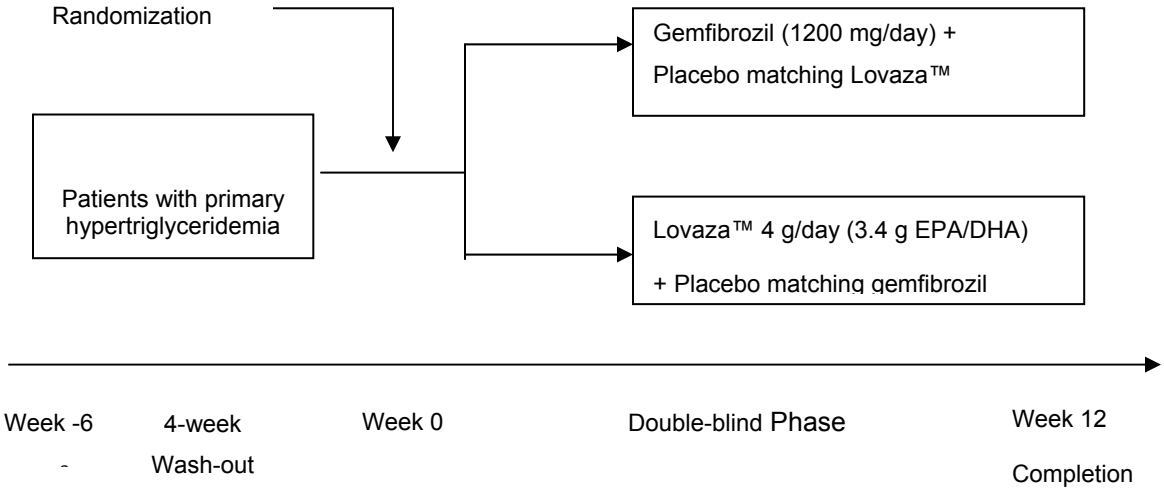
Safety*:* Eight patients were withdrawn from the study because of adverse events: 3 from the Lovaza™ group (one each with endometrial carcinoma, head injury, and cataract operation) and 5 from the placebo group (1 with elective coronary surgery, 1 with myocardial infarction, and 3 with angina). The causal relationship of these adverse events to the treatment was not stated in the publication. Diastolic blood pressure decreased from a baseline level of 86 ± 11 mm Hg to 80 ± 12 mm Hg ($P < .02$) after treatment with Lovaza™, which was also lower than in the placebo group (84 ± 12 mm Hg to 82 ± 10 mm Hg, $P < .05$). No changes in fasting blood glucose were observed in either group.

Conclusion: The study concluded that Lovaza™ was effective in lowering serum TG and VLDL-C levels in patients with primary hypertriglyceridemia and may be used as a TG-lowering agent.

Stalenhoef AFH, de Graaf J, Wittekoek ME, Bredie SJH, Demacker PNM, Kastelein JJP. The effect of concentrated n-3 fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidazability in patients with hypertrygliceridemia. *Atherosclerosis* 2000;153:129-138.[84]

Study Design: Stalenhoef et al. conducted a randomized, double-blind, double-dummy study to compare the effect of gemfibrozil versus Lovaza on lipid, lipoproteins, and LDL subfraction profile in patients with primary hypertriglyceridemia. This study was supported by a grant from Pronova Biocare, Oslo, Norway. Study design is shown in Figure 1.

Figure1. Study design



[a]Lipid-lowering medications were discontinued.

Inclusion criteria*:* Patients with primary hypertriglyceridemia (plasma TG levels between 356 mg/dL (4 mmol/L) and 2492 mg/dL (28 mmol/L).

Exclusion criteria: Secondary causes of dyslipidemia, including history of diabetes mellitus, or apolipoprotein phenotype E2/E2.

Tests performed: Plasma lipid levels were measured at weeks -2, 0, 6, 10 and 12. For safety assessment, serum ALAT, ASAT, glucose, and hemoglobin A_{1c} levels were measured.

Outcome measure: To compare the effects of Lovaza vs gemfibrozil on LDL heterogeneity in patients with hypertriglyceridemia

Baseline clinical characteristics including BMI, lipid parameters, fasting blood glucose, and hemoglobin A_{1c} levels were similar among patients in the treatment groups. Patients continued their standard lipid-lowering diet throughout the trial; however, vitamin supplements, antioxidants, or oral blood glucose lowering agents were not consumed.

Results: Data from 28 patients were included in the analysis; 1 patient (Lovaza™ group) developed excessive hypertriglyceridemia after discontinuing the regular medication, and another patient (gemfibrozil group) was not willing to continue after randomization.

Treatment with gemfibrozil and Lovaza™ resulted in significant reductions in the levels of plasma TG, VLDL-C, VLDL-TG, whereas HDL-C and LDL-C were increased compared with baseline; however, the differences were not significant between the treatment groups (Table 1).

Significant increases were found in the cholesterol content of LDL-C1, LDL-C2 and LDL-C3 after treatment with Lovaza™ and gemfibrozil resulting in a more buoyant LDL subclass distribution, as indicated by a rise in the K-value: +10% ($P < .05$) and +27% ($P < .01$), respectively from baseline levels.

Table 1. Changes in Lipid Parameters and LDL Subfraction Profile (K-value) After Treatment with Lovaza™ and Gemfibrozil

	Lovaza™ (n = 15)			**Gemfibrozil (n = 13)**		
	Baseline	Week 12	Δ *(%)* *P*-value[b]	Baseline	Week 12	Δ *(%)* *P*-value[b]
TC						
mg/dL[a]	345.15 ± 117	306 ± 90	-9 ± 15	279 ± 62	252 ± 45	-7 ± 15
mmol/L	8.85 ± 3.0	7.85 ± 2.32	<.05	7.15 ± 1.6	6.47 ± 1.2	.06
TG						
mg/dL[a]	871 ± 579	466 ± 249	-37 ± 26	623 ± 261	319 ± 202	-40 ± 53
mmol/L	9.79 ± 6.51	5.24 ± 2.8	<.001	6.99 ± 3	3.58 ± 2.3	.01
HDL-C						
mg/dL[a]	28 ± 7	30 ± 7	11 ± 19	31 ± 6	35 ± 7	17 ± 21
mmol/L	0.71 ± 0.17	0.77 ± 0.18	<.05	0.79 ± 0.16	0.91 ± 0.2	<.05
VLDL-C						
mg/dL[a]	202 ± 124	132 ± 92	-33 ± 22	126 ± 54	62 ± 30	-40 ± 55
mmol/L	5.17 ± 3.17	3.38 ± 2.37	<.001	3.23 ± 1.38	1.58 ± 0.8	<.01
VLDL-TG						
mg/dL[a]	780 ± 532	397 ± 206	-39 ± 27	554 ± 241	266 ± 195	-42 ± 60
mmol/L	8.76 ± 5.98	4.46 ± 2.31	<.001	6.22 ± 2.71	3 ± 2.19	.01
LDL-C						
mg/dL[a]	116 ± 40	144 ± 39	30 ± 31	122 ± 34	155 ± 44	34 ± 50
mmol/L	2.97 ± 1.03	3.7 ± 1.0	.005	3.13 ± 0.87	3.98 ± 1.1	<.05
K-Value[c]	-0.61 ± 0.13	-0.55 ± 0.16	10 ± 22 .05	-0.61 ± 0.11	-0.45 ±0.2	27 ± 33 <.01

Data are expressed as mean ± SD

[a]Data presented in mmol/l (except parameter K) were converted to mg/dL: conversion factors—TG (x89), VLDL-TG (x89), TC (x39), lipoproteins (x39).

[b]*P*-value for within treatment groups, Wilcoxon signed ranks test.

[c]K-value is a continuous variable indicating the contribution of each LDL subfraction expressed by its cholesterol content (%LDL-C_1 to %LDL-C_5) relative to the concentration of total LDL (total LDL = sum of %LDL-C_1 to %LDL-C_5).

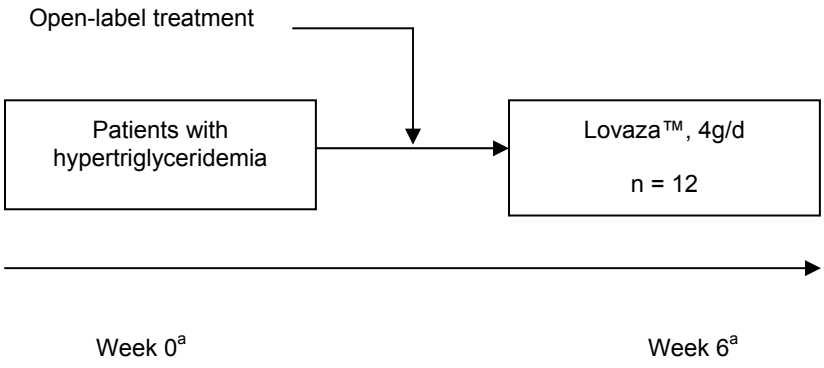
Safety: Lovaza™ and gemfibrozil were well tolerated by all patients and no significant adverse events were reported.

Conclusion: The authors concluded that both Lovaza™ and gemfibrozil have favorable anti-atherogenic properties on lipid and lipoprotein levels and LDL subfraction profile.

3.24 Westphal S, Orth M, Ambrosch A, Osmundsen K, Luley C. Postprandial chylomicrons and VLDLs in severe hypertriacylglycerolemia are lowered more effectively than are chylomicron remnants after treatment with n-3 fatty acids. *Am J Clin Nutr* 2000;71:914-20.[66]

Study Design: Westphal et al conducted an open-label study in patients with hypertriglyceridemia to evaluate the effect of Lovaza™ in lowering lipoproteins, including large and small chylomicron remnants in postprandial state. A combination of size exclusion chromatography and fluorometery was used to separate lipoproteins and chylomicrons before and after oral fat tolerance test.

Figure 1. Study Design



[a] Oral fat tolerance test was performed before and after treatment.

Inclusion criteria: Patients (mean age of 46 ± 6 years and BMI of 27.7 ± 7kg/m^2) with hypertriglyceridemia were recruited; fasting TG levels >300 mg/dL (3.4 mmol/L).

Exclusion criteria: Age >65 years, Type III hyperlipoproteinemia, thyroid dysfunction, fasting blood glucose >140 mg/dL (7.8 mmol/L), alcohol abuse (>2 drinks/d), serum creatinine >2.0 mg/dL (176.8 μmol/L), serum ALT >3 x upperlimit of the normal range, consumption of fish meals >1 time/week, and

treatment with lipid-lowering agents or omega-3 supplements prior to 2 months of enrollment.

Tests performed: Oral fat tolerance test before and after treatment. Blood samples were drawn in the fasting state and until 8 h postprandially. Serum lipid parameters and lipoprotein lipase levels were measured.

Outcome measures: Changes in serum lipids including chylomicron remants.

Results: All patients completed the study. Treatment with Lovaza™ resulted in significant rise in the EPA and DHA content of serum phospholipids (Table 1).

In the fasting state, treatment with Lovaza™ significantly lowered VLDL-TG (-44%), VLDL-C (-40%), TC (-14%) and increased LDL-C (+45%) from baseline (before treatment) levels. No significant difference was noted in the levels of HDL-C or lipoprotein lipase (Table 1).

Table 1. Effect of Lovaza™ on Fasting Lipids

	Before	After
TC		
mg/dL[a]	366.6 ± 35.1	312 ± 19.5
mmol/L	9.4 ± 0.9	8.0 ± 0.5
TotalTG		
mg/dL[a]	1210.4 ± 231.4	729.8 ± 142.4*
mmol/L	13.6 ± 2.6	8.2 ± 1.6
VLDL-TG		
mg/dL[a]	1201.5 ± 249.2	676.4 ± 169.1*
mmol/L	13.5 ± 2.8	7.6 ± 1.9
HDL-C		
mg/dL[a]	34.3 ± 2.3	35.9 ± 2.7
mmol/L	0.88 ± 0.06	0.92 ± 0.07
VLDL-C		
mg/dL[a]	230.1 ± 39	128.1 ± 27.3*
mmol/L	5.9 ± 1.0	3.3 ± 0.7
LDL-C		
mg/dL[a]	101.4 ± 27.3	148.2 ± 27.3*
mmol/L	2.6 ± 0.7	3.8 ± 0.7
L. Lipase		
μg/L	488 ± 31	544 ± 45

[a]Data reported in mmol/L were converted to mg/dL: conversion factors—TGx89, TC, HDL-C, LDL-C, VLDL-C x 39.
* Indicates significant difference from before treatment values, $P < .05$.

In the postprandial state, treatment with Lovaza™ resulted in significant reductions in serum TG levels (-32% to -39%; $P < .05$) at all time points (0, 4, 6, and 8 h of the oral fat tolerance test) compared with before treatment levels. The TG content in VLDL and chylomicrons were significantly reduced: VLDL-TG levels were reduced by 36-43% ($P<.05$), whereas in chylomicrons the TG content decreased by 49%, 58%, and 64% at 4, 6, and 8 h, respectively ($P < .05$), compared with before treatment levels. Chylomicron remants were reduced only in the late postprandial phase: at 8 h, large remants were reduced by -43% ($P < .05$) and small remnants by -31% ($P < .05$), compared with before treatment levels.

Safety: No adverse events were reported.

Conclusion: The study concluded that treatment with Lovaza™ effectively lowered chylomicrons and VLDLs; however the lowering effect of chylomicron remnants was observed only in late postprandial

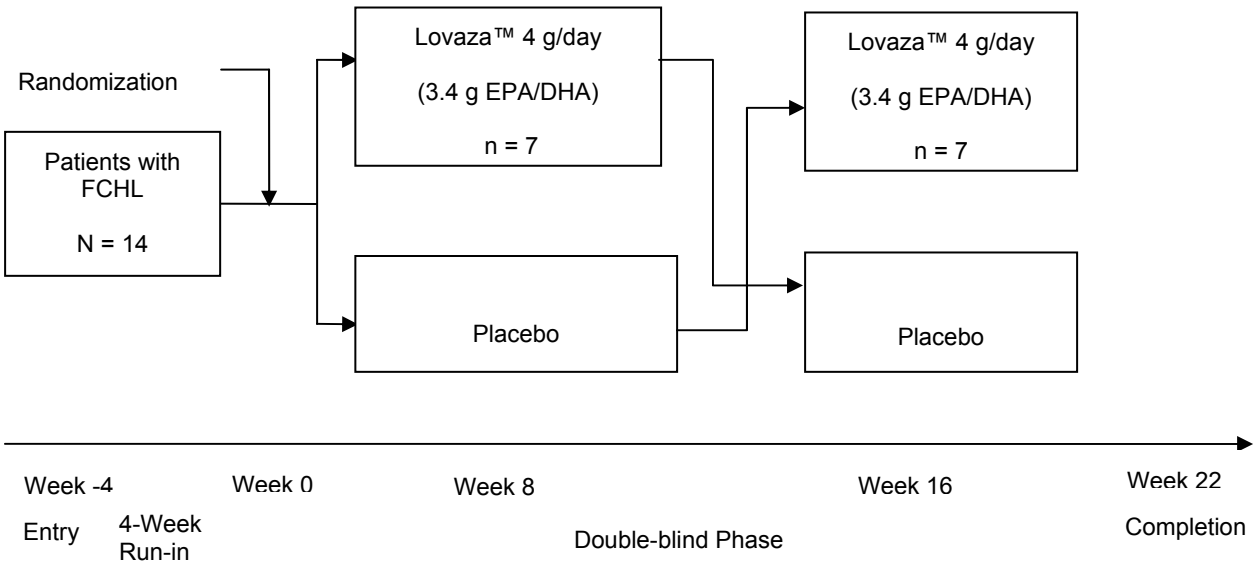
phase.

3.3 Lovaza™ Monotherapy at Doses of 4 g/d: Patients with Familial Combined Hyperlipidemia

3.31 Calabresi L, Donati D, Pazzucconi F, Sirtori CR, Franceschini G. Lovaza in familial combined hyperlipidemia: effects of lipids and low density lipoprotein subclasses. Atherosclerosis 2000;148:387-96.[62]

Study Design: Calabresi et al conducted a randomized, double-blind, crossover trial to evaluate the effect of Lovaza™ on lipid and lipoprotein parameters, and LDL subclass distribution in patients with familial combined hyperlipidemia (FCHL). The study was supported in part by a grant from Pronova Biocare, Oslo, Norway. Study design is shown in Figure 1.

Figure 1. Study Design



Inclusion criteria*:* Patients with FCHL were diagnosed based on the following criteria: TC and/or TG exceeding the 90th percentile in the general population adjusted for age and sex. Presence of hyperlipidemia for at least 1 year with LDL phenotype B as defined by a major LDL particle subpopulation with a diameter <25.5 nm. At least one first-degree relative diagnosed with hyperlipidemia different from the subject.

Exclusion criteria: Patients with a plasma Lp(a) concentration > 30 mg/dL.

Tests performed: Plasma lipid and lipoprotein levels were monitored at weeks -4, -2, 0, 4, 8, 12, 16, and 22 corresponding to visits -2,-1, 0, and 1 to 5. Baseline values: because lipid levels varied substantially

during baseline period individual values measured for each patient at visits -2, -1, and 0 were averaged before comparison. Treatment values: individual plasma lipid and lipoprotein levels were averaged after 4 and 8 weeks of treatment with Lovaza or placebo before comparison.

All patients were on standard low fat (30% of calories) diet for at least 6 months prior to study entry and lipid-lowering medications were terminated at least 3 months before enrollment.

Patient characteristics and lipid values were similar at randomization.

Outcome measures: Changes in lipid and lipoprotein parameters, and LDL subclass distribution.

Results: Thirteen patients successfully completed the trial: 1 patient could not complete the final assessment at week 22 due to an emergency hospitalization.

Treatment with Lovaza™ resulted in a significant reduction in plasma TG levels compared with baseline and placebo (-27% and 21%, respectively); Table 1. Plasma VLDL-C levels were significantly reduced after treatment with Lovaza™ compared with baseline and placebo (-18% and -29%, respectively), whereas LDL-C levels were increased by 25% relative to placebo.

Table 1. Plasma Lipid and Lipoprotein Levels at Baseline and After Treatment

Lipids/lipoproteins	Baseline	Placebo	Lovaza™
TC			
mg/dL	270.7 ± 33.1	266 ± 38.9	282.5 ± 44
mmol/L[b]	6.94 ± 0.84	6.82 ± 0.99	7.24 ± 1.12
VLDL-C[a]			
mg/dL	40 (30-206)	46 (20-199)	33 (22-92)[c]
mmol/L[b]	1.0 (0.76-5.28)	1.17 (0.5-5.1)	0.83 (0.56-2.35)[c]
LDL-C			
mg/dL	167.1 ± 47.6	161.5 ± 50.6	202.7 ± 45.8[d]
mmol/L[b]	4.28 ± 1.2	4.14 ± 1.29	5.19 ± 1.17[d]
HDL-C			
mg/dL	41.5 ± 11.5	39.7 ± 10	42.5 ± 14.7
mmol/L[b]	1.06 ± 0.29	1.01 ± 0.25	1.08 ± 0.37
TG[a]			
mg/dL	251.1 (141-779)	231.8 (149-1030)	183.5 (75- 407)[c]
mmol/L[b]	2.82 (1.58-8.75)	2.6 (1.67-11.57)	2.06 (0.84-4.57)[c]
Apo A1			
mg/dL	108.8 ± 27.2	113.5 ± 19.6	112.1 ± 26.8
Apo B			
mg/dL	135.2 ± 21.1	134.1 ± 26.1	143.8 ± 23.6[c]

Data are presented as mean ± SD except when indicated[a], which are median and range.
[b]Data reported in mg/dL were converted to mmol/L: conversion factors – TG (/ 89), TC (/39), lipoproteins (/39).
[c]Significantly different from baseline and placebo, P <.05.
[d] Significantly different from placebo, P <.05.

LDL composition and subclass distribution: Treatment with Lovaza™ resulted in significant changes in LDL composition and subclass distribution, whereas placebo had no significant effect. Unesterified cholesterol content of LDL increased from 8.9 ± 0.9% at baseline to 9.5 ± 0.9% after treatment with Lovaza™, compared with 8.8 ± 0.6% after placebo (P < .05); cholesteryl ester content of LDL increased from 39.06 ± 4.14% to 40.35 ± 2.67% after treatment with Lovaza™, compared with 38.4 ± 4.6% after

treatment with placebo ($P < .05$). The TG and phospholipid levels in LDL were reduced from baseline in patients treated with Lovaza™, although the differences were not statistically significant.

Treatment with Lovaza™ resulted in changes in LDL subclass distribution: plasma levels of IDL and subclasses LDL1 and LDL2 were increased from baseline, whereas LDL3 levels were decreased (Table 2). The size of small LDL particles at baseline ranged from 23.5 nm to 25.3 nm with a mean diameter of 24.9 ± 0.3 nm; however, no significant changes were noted in particle size after treatment with Lovaza™ or placebo (25 ± 0.3 nm and 24.8 ± 0.5 nm, respectively).

Table 2. LDL Subclass Distribution at Baseline and After Treatment. Data are presented as mean concentrations (mg/dL) of Apo B ± SD.

LDL subfractions mg/dL	Baseline	Placebo	Lovaza™
IDL	18.6 ± 4.4	19.7 ± 8.3	23.3 ± 6.9*
LDL-1	14 ± 3.1	15.2 ± 7.4	20.3 ± 10.2
LDL-2	28.5 ± 7.5	27.6 ± 10.5	36 ± 11.5*
LDL-3	49.7 ± 12.1	41.9 ± 14.5	40 ± 17.3

*Significantly different from baseline and placebo, $P < .05$.

Safety*:* Lovaza™ was well tolerated. No drug-related adverse events were reported, and no patient discontinued treatment because of side effects. Treatment with Lovaza did not affect plasma glucose levels, uric acid, liver enzymes, kidney function, or platelet counts. Patients' body weight and blood pressure did not change significantly during the study.

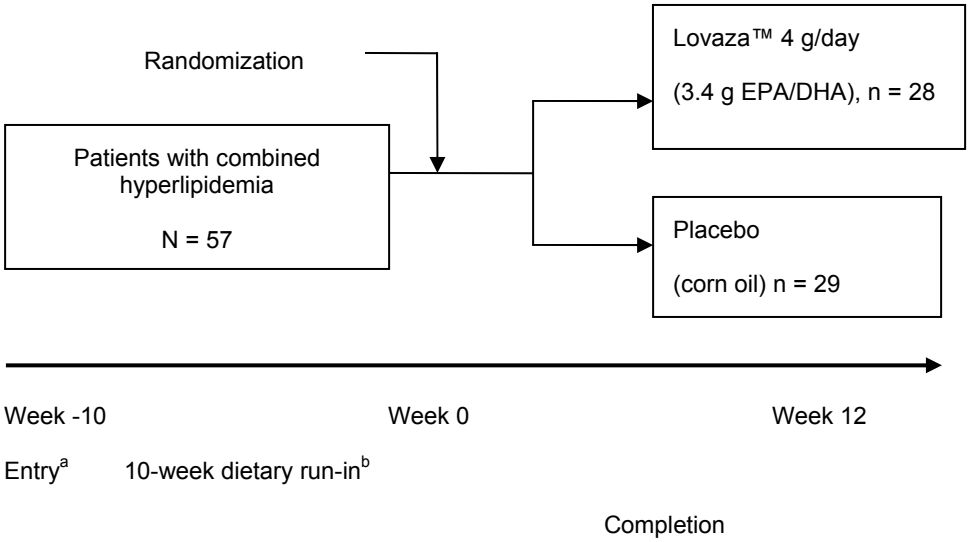
Conclusion: The study concluded that Lovaza™ effectively lowered plasma TG and VLDL levels in patients with FCHL and redistributed LDL subfractions from dense to buoyant LDL particles; however, the size of LDL particles was not affected by the treatment suggesting that the LDL size in FCHL was independent of plasma lipid/lipoprotein levels.

3.4 Lovaza™ 4 g/d Monotherapy: Patients with Combined Hyperlipidemia

3.41 Grundt H, Nilsen DWT, Hetland O, Aarsland T, Baksaas I, Grande T, Woie L. Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. *J Intern Med 1995;237:249-59.*[85]

Study Design: Grundt et al conducted a randomized, double-blind, placebo-controlled study to assess the efficacy of Lovaza™ monotherapy on serum lipids and lipoproteins in patients with combined hyperlipidemia. The study was supported by Pronova, Norway and by Phillips Petroleum Co., Norway. Study design is shown in Figure 1.

Figure 1. Study Design



[a]A total of 141 patients were enrolled.

[b]After the dietary run-in period, 79 patients did not continue to meet the inclusion criteria with regard to serum TG/TC levels, whereas 5 patients were not eligible for personal, administrative, or medical reasons. Fifty-seven patients entered the intervention phase; however, 1 patient was withdrawn for administrative reasons.

Inclusion criteria: Patients, aged between 18 to 70 years, with combined hyperlipidemia and mean change in body weight of less than 1 kg/week during the dietary run-in period; serum TG levels between 2 mmol/L (178 mg/dL) and 15 mmol/L (1335 mg/dL); and TC ≥6 mmol/L (234 mg/dL).

Exclusion criteria: Use of dietary supplement, medication containing omega-3 fatty acids, or antihyperlipemic medication during the run-in period; myocardial infarction or other serious illness in the preceding 3 months of trial entry; diabetes mellitus, serious psychological illness, known drug or alcohol abuse, pregnancy, and lactation as well as clinically significant biochemical anomalies based on laboratory tests.

Tests performed: serum TG, TC, and HDL-C levels were measured at weeks −10, −4, −2, 4, 8, and 12. In addition, blood pressure, heart rate, body mass index (BMI), insulin, proinsulin, hemoglobin, erythrocyte sedimentation rate, serum glucose, aspartate aminotransferase, alanine aminotransferase, and creatinine levels were measured.

Outcome measures: changes in blood lipids and lipoprotein levels in patients with hyperlipidemia. Baseline clinical characteristics, including serum glucose, insulin levels, and lipid parameters were similar between groups, except for erythrocyte sedimentation rate, which varied significantly: mean 13.1 ± 7.9 mm/h vs 9.4 ± 6.7 mm/h for Lovaza and placebo groups, respectively ($P < .05$).

Results: Fifty-six patients completed the study. Treatment with Lovaza™ reduced baseline serum TG by 28% reaching statistical significance by 4 weeks of therapy (Table 1). A decrease in serum TC and an increase in HDL-C were observed in both treatment groups.

Table 1. Change in Lipid Parameters in Lovaza™ and Placebo Treatment Groups

	Lovaza™		**Placebo**	
	Baseline	% Change at Week 12	Baseline	% Change at Week 12
TG				
mmol/L	4.0 ± 2.2	−28%[b,c]	3.1 ± 1.2	Non-significant decrease
mg/dL[a]	356 ± 196		276 ±107	
HDL-C				
mmol/L	0.9 ± 0.2	10%[d]	0.9 ± 0.2	5%
mg/dL[a]	35 ± 8		35 ± 8	

Values are presented as mean ± SD.
[a]Data reported in mmol/L were converted to mg/dL: conversion factors—TG (×89) and HDL-C (×39).
[b]*P* < .05 for significance of change within group, Student's t test.
[c]*P* < .05 for significance of change between treatment groups, Student's t test.
[d]*P* < .05 for significance of change within group at weeks 4 and 8, Student's t test

Safety: Side effects were all mild and mainly involved gastrointestinal complaints. No difference was found in the incidence of side effects between treatment groups. Fasting serum glucose and plasma insulin levels remained unchanged in both groups. However, patients in the Lovaza™ group showed a significant decrease in both systolic (baseline: 129 ± 15.6 mm Hg, decrease: 8 mm Hg; *P* < .05) and diastolic (baseline: 84.2 ± 9.1 mm Hg, decrease: 4 mm Hg; *P* < .05) blood pressure and heart rate during the 12-week intervention period. No significant changes in blood pressure were noted in the placebo group (baseline systolic: 128.3 ± 14.2 mm Hg, baseline diastolic: 86.6 ± 7.4 mm Hg).

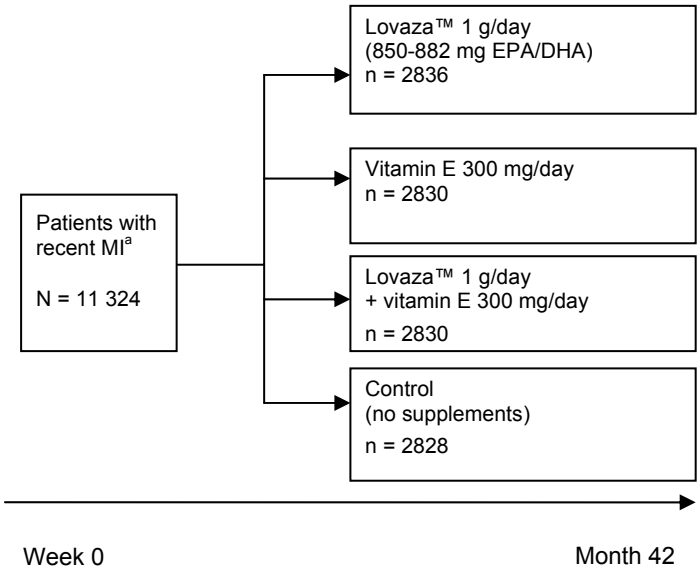
Conclusion: The study concluded that 12 weeks of treatment with Lovaza™ 4 g/day significantly reduced serum lipids, blood pressure, and heart rate in patients with combined hyperlipidemia and thereby improved the atherogenic risk profile in these patients.

3.5 Lovaza™ Monotherapy: Secondary Prevention Post Myocardial Infarction

3.51 GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and Vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. *Lancet* 1999; 354:447-55.[10]

Study Design: Marchioli et al conducted a randomized, open-label, parallel-group, multicenter, prospective study to evaluate the independent and combined efficacies of Lovaza™ and vitamin E on morbidity and mortality in patients with a recent history of myocardial infarction (≤3 months). Study design is shown below.

Figure 1. Study design



[a]Patients were followed-up at 6, 12, 18, 30, and 42 months. Patients continued with the recommended preventive medication including beta-blockers, aspirin, and inhibitors of angiotensin-converting enzymes.

Inclusion criteria: Patients with recent (<3 months) MI, who were able to provide informed written consent

Exclusion criteria: Known congenital defects of coagulation, known allergy or contraindications to Lovaza or vitamin E, unfavorable short-term outlook (congestive heart failure, cancer etc).

Tests performed: Blood lipids (TC, TG, LDL-C and HDL-C) were measured at baseline and at follow-up visits (6, 12, 18, 30, and 42 months).

Outcome measures: Primary combined efficacy endpoints were cumulative rate of all-cause death, non-fatal MI, and non-fatal stroke; and cumulative rate of cardiovascular death, non-fatal MI, and non-fatal stroke.

Baseline demographic and clinical characteristics were well balanced across the treatment groups. Dietary habits, secondary prevention treatments, and revascularization procedures at study entry and during intervention were similar among groups.

Results: Treatment with Lovaza™ resulted in a small but significant decrease (-3.4%) in TG levels, compared with the control group. No significant changes were noted in other blood lipid levels compared with baseline values.

Treatment with Lovaza™ significantly lowered the risk of combined primary endpoint of death, nonfatal MI, and nonfatal stroke by 15% compared with the control group (*P*= .023, 4-way factorial analysis); the relative decrease in risk for cardiovascular death, nonfatal MI and nonfatal stroke was 20% (*P*=.008) compared with the control group. No added benefit was apparent with the combined vitamin E treatment

Table 1. Effect of Treatment with Lovaza™ on Primary and Secondary Endpoints.

	Relative risk (95% CI) of Lovaza™ vs control: 2-way analysis	**Relative risk (95% CI) of Lovaza™ vs control: 4-way analysis**
PRIMARY ENDPOINTS		
Death, non-fatal MI and non-fatal stroke	0.90 (0.82 – 0.99), (p=0.048)	0.85 (0.74 – 0.98) (p=0.023)
Cardiovascular death, non-fatal MI, non-fatal stroke	0.89 (0.80 – 1.01), (p=0.053)	0.80 (0.68 – 0.95) (p=0.008)
SECONDARY ENDPOINTS		
All fatal events	0.86 (0.76 – 0.97)	0.80 (0.67 – 0.94)
Cardiovascular deaths	0.83 (0.71 – 0.97)	0.70 (0.56 – 0.87)
Cardiac death	0.76 (0.65 – 0.92)	0.65 (0.51 – 0.82)
Coronary death	0.80 (0.67 – 0.96)	0.65 (0.51 – 0.84)
Sudden death	0.74 (0.58 – 0.93)	0.55 (0.40 – 0.76)
Other deaths	0.91 (0.74 – 1.11)	0.99 (0.75 – 1.30)
Non-fatal cardiovascular events	0.98 (0.83 – 1.15)	0.96 (0.76 – 1.21)
CHD death and non-fatal MI	0.87 (0.76 – 0.99)	0.75 (0.62 – 0.90)
Fatal and non-fatal stroke	1.21 (0.91 – 1.63)	1.30 (0.87 – 1.96)

Non-fatal MI was diagnosed if at least 2 of the following were present: chest pain of typical intensity and duration; elevation or depression of ST segment by 1 mm or more in any lead limb of the ECG, of 2 mm or more in any precordial lead or both; doubling in necrosis enzymes. Diagnosis of non-fatal stroke required unequivocal signs of neurological deficit with sudden onset and a duration of more than 24 hr.

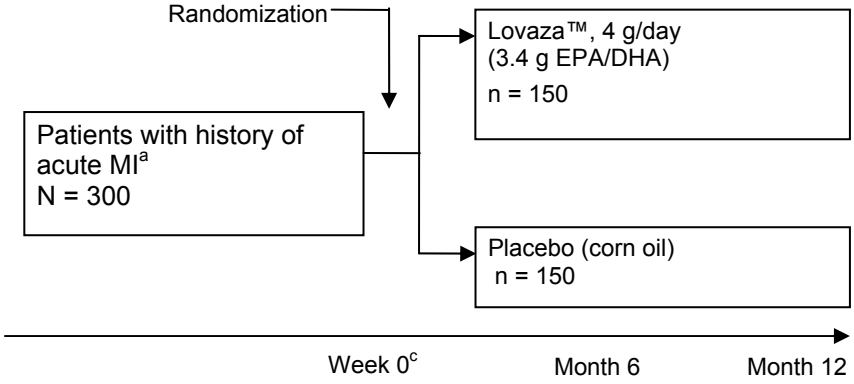
Safety: Gastrointestinal disturbances and nausea were the most frequently reported side-effects (4.9% and 1.4%, respectively in Lovaza™ group; 2.9% and 0.4%, respectively in vitamin E group). Cancer was reported with equal prevalence in all treatment groups.

Conclusions: The study concluded that treatment with Lovaza™ resulted in a clinically important and statistically significant benefit, whereas vitamin E had no benefit.

3.52 Nilsen DWT, Albrelasen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentration of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001; 74:50-6.[86]

Study Design: Nilsen et al conducted a randomized, double-blind, placebo-controlled study to evaluate the effect of Lovaza™ on serum lipids and subsequent cardiac events in patients with a recent history of acute myocardial infarction. This study was supported by Pharmacia A/S and Pronova A/S, Norway. Study design is shown in Figure 1.

Figure 1. Study Design



[a] Study entry was between days 4 and 6 after MI.
[b] Dose: 2 capsules twice daily.
[c] Other fish oil supplements were discontinued before intervention.

Inclusion criteria: Patients, aged 18 years and above, with a history of acute MI verified by WHO criteria

Exclusion criteria*:* Non-compliance to protocol, life expectancy <2 years because of heart failure, malignancy or other reasons, gastrointestinal bleeding and/or stomach ulcer, blood platelets 100 × 109/L, liver insufficiency, involvement in another study and residence outside the recruitment area

Tests performed: Serum lipid parameters were measured at week 0, 6 weeks, 6 months, 1 year, 18 months and for some patients after 2 years. Clinical examination and electrocardiogram were also performed.

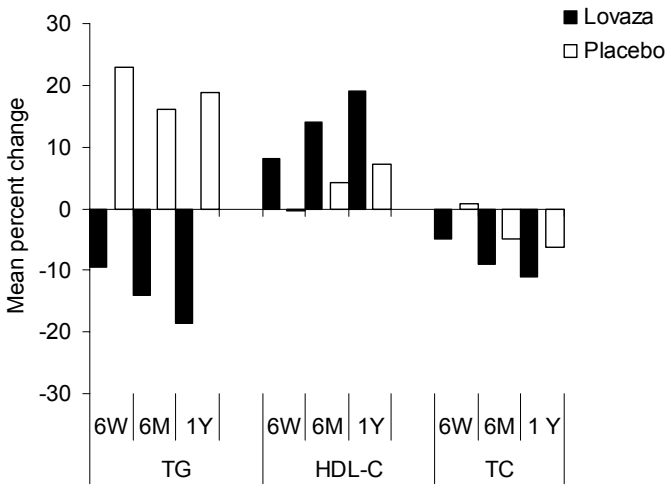
Outcome measures: Changes in serum lipid levels and cardiac event rates

Baseline demographics, clinical characteristics, and the use of concomitant medications were not significantly different between groups.

Results: Eighty-two percent of patients in the Lovaza™ group and 86% in the placebo group were drug compliant after 6 weeks, as assessed by capsule counting.

Treatment with Lovaza™ significantly reduced serum TG levels and increased HDL-C levels from baseline compared with placebo measurements. (Figure 1). Twenty-eight percent of patients in the Lovaza™ group and 24% in the placebo group experienced at least 1 cardiac event during the follow-up period (hazard ratio between Lovaza™ and placebo groups: 1.19); cardiac events were defined as death, resuscitation, recurrent MI, and unstable angina. However, no significant difference was found between the groups in number, type, or severity of the event

Figure 2. Change in Serum Lipids Over time



Safety: Forty-two patients in the Lovaza™ group and 36 patients in the placebo group experienced at least 1 cardiac event; unstable angina was the most common type among the predefined cardiac events followed by recurrent MI.

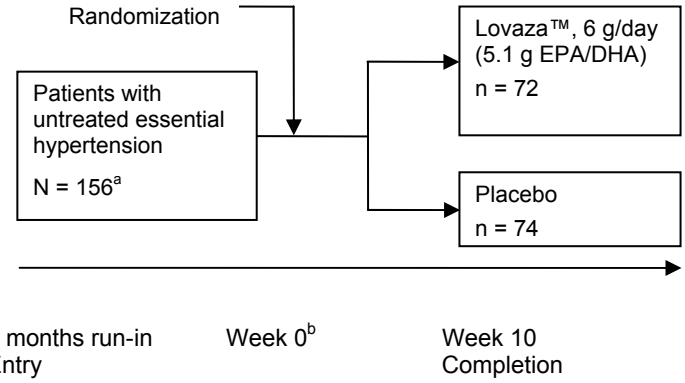
Conclusion: The study concluded that treatment with Lovaza™ significantly reduced serum TG and increased HDL-C levels from baseline compared with placebo measurements; however, administration of Lovaza™ early after an acute MI had no significant benefit in clinical prognosis compared with placebo.

3.6 Lovaza™ Monotherapy at Doses Exceeding 4 g/d: Additional Safety and Efficacy Studies in Healthy Subjects

3.61 Bønaa KH, Bjerve KS, Nordoy A. Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. *Arteriosclerosis and Thrombosis* 1992;12:675-681.[87]

Study Design: Bønaa et al conducted an additional posthoc analysis using samples and data from a previous study to assess the effect of Lovaza™ (K85) on serum lipid parameters in patients with untreated, stable essential hypertension. The study was randomized, double-blind, and placebo-controlled. Study design is shown in figure 1; for details refer to the previous study.

Figure 1. Study Design



[a]Data analysis was based on 146 subjects.
[b]Patients were required to continue their usual diet and lifestyle.

Inclusion criteria: Patients, aged between 34 and 60 years, with untreated, stable essential hypertension were included; patients were not previously treated with lipid-lowering or antihypertensive drugs. All patients had serum TC levels between 203 mg/dL (5.2 mmol/L) and 390 mg/dL (10.0 mmol/L); mean diastolic blood pressure between 85 and 110 mmHG; mean systolic blood pressure below 180 mmHg. Clinical examination, laboratory tests and ECG were performed to determine the health of the patients.

Exclusion criteria: Cardiovascular disease, bleeding disorder, diabetes mellitus, disabling chronic disease, psychopathologic disease, alcoholism, obesity (BMI >32)**.**

Tests performed: Serum lipid parameters and EPA/DHA content of plasma phospholipids were measured at week 0 and at study end.

Outcome measures: Changes in serum lipid parameters.

Baseline lipid parameters were similar among patients in the 2 treatment groups.

Results: All patients completed the study; however, data from 10 patients were not included in the analysis as 2 patients were treated with corticosteroids, 3 patients were treated with antibiotics, and 5 patients did not have data on fatty acids.

After 10 weeks of treatment with Lovaza™, significant increases were found in the EPA and DHA content of plasma phospholipids compared with placebo (Table 1).

Treatment with Lovaza™ resulted in a significant reduction in plasma TG levels from baseline compared with no change in the placebo group (Table 1). The decrease in serum TG levels correlated significantly with the increase in EPA and DHA levels: EPA ($r = -0.3$, $P < .05$), DHA ($r = -0.27$, $P < .05$). Significant increases were also noted in HDL-C levels, which rose by 1.95 mg/dL (0.05 mmol/L) in the Lovaza™ group compared with 3.12 mg/dL (0.08 mmol/L) in the placebo group (Table 1). The increase in HDL-C levels after Lovaza™ administration correlated significantly with the change in plasma EPA levels ($r = 0.33$, $P = .006$); in the placebo group an inverse correlation was found between the change in serum HDL-C and plasma DHA levels.

Table 1. Change in Serum TG Levels after Treatment with **Lovaza** or Placebo.

	Lovaza™		**Placebo**	
	Baseline	Week 10	Baseline	Week 10
TG				
mg/dL[a]	124.6 ± 68.5	97.9 ± 49.8***[c]	132.6 ± 100.6	129.1 ± 89
mmol/L	1.40 ± 0.8	1.10 ± 0.6	1.49 ± 1.1	1.45 ± 1.0
TC				
mg/dL[a]	253.9 ± 39.8	254.7 ± 36.3	256.6 ± 31.2	255.1 ± 34.3
mmol/L	6.51 ± 1.0	6.53 ± 0.9	6.58 ± 0.8	6.54 ± 0.9
LDL-C				
mg/dL[a]	178.6 ± 38.2	182.5 ± 36.3	177.1 ± 30.8	174.3 ± 33.2
mmol/L	4.58 ± 1.0	4.68 ± 0.9	4.54 ± 0.8	4.47 ± 0.9
HDL-C				
mg/dL[a]	51.1 ± 16.4	53.0 ± 17.9*	51.5 ± 12.9	54.6 ± 14.4**
mmol/L	1.31 ± 0.4	1.36 ± 0.5	1.32 ± 0.3	1.40 ± 0.4
Apo A-1 (g/L)	1.55 ± 0.3	1.54 ± 0.3[b]	1.56 ± 0.2	1.62 ± 0.3
Apo B (g/L)	1.53 ± 0.3	1.49 ± 0.2	1.54 ± 0.3	1.51 ± 0.3
EPA[e]	3.4 ± 2.1	8.5 ± 2.5***[d]	3.2 ± 2.3	2.4 ± 1.3
DHA[e]	8.4 ± 2.1	10.1 ± 1.8***[d]	8.3 ± 1.9	7.7 ± 1.8

Data are presented as mean ± SD.
[a]Data reported in mmol/L were converted to mg/dL: conversion factors—TGx89, TCx39, HDL-C and LDL-C x 39.
[b, c, d] indicate significant difference between treatment groups: $P < .05$, $P < .01$, $P < .001$.
[e]EPA and DHA are expressed as percentage of total fatty acids of plasma phospholipids.
*, **, *** indicate significant difference within group: $P < .05$, $P < .01$, $P < .001$.

Safety: Two patients were treated with corticosteroids and 3 patients were treated with antibiotics for febrile infectious diseases. Mild to moderate abdominal discomfort was reported by 10 patients in the Lovaza™ group and 7 patients in the placebo group.

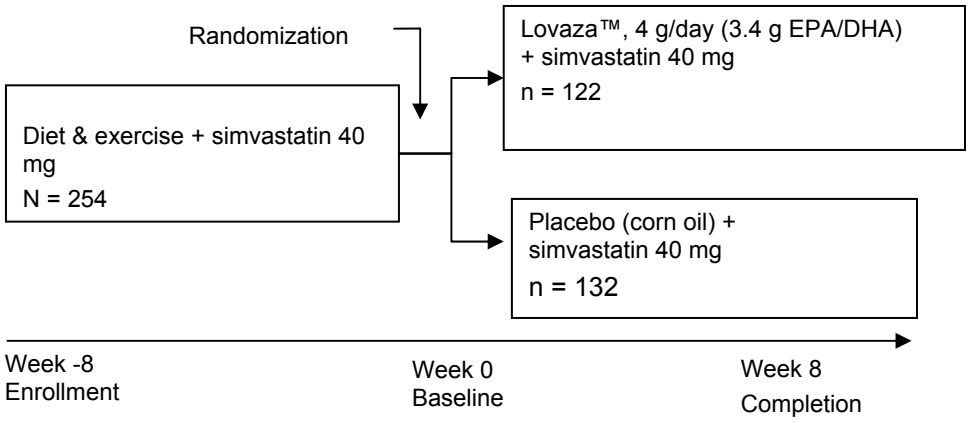
Conclusion: The study indicated that treatment with Lovaza™ resulted in differences in the content of EPA and DHA that correlated significantly in relation to both HDL-C and apo A-1 levels.

3.7 Lovaza™ Combination Therapy with Statins: Safety and Efficacy

3.71 Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clinical Ther.* 2007;29(8):1-14.[79]

Study Design: Davidson et al conducted a multicenter, randomized, double-blind, placebo-controlled study to assess whether therapeutic doses of EPA+DHA can further reduce non–HDL-C in patients with persistent hypertriglyceridemia on stable statin therapy. Study design is shown in Figure 1.

Figure 1: Study Design



Inclusion criteria: Men and women aged 18 to 79 years on statin therapy who were at or within 10% of their NCEP ATP III LDL-C goals during the lead-in who had persistent hypertriglyceridemia (TG 200 to 499 mg/dL; 2.2 to 5.6 mmol/L).

Exclusion criteria: Use of any non–study-related lipid-altering drugs including statins, bile acid sequestrants, cholesterol absorption inhibitors, fibrates or non–study-related omega-3 fatty acids supplements, or other supplements known to alter lipid metabolism. History of cardiovascular event (i.e. myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, unstable congestive heart failure requiring a change in treatment) or revascularization procedure in the 6 months prior to enrollment. Poorly controlled diabetes mellitus (HbA1C > 8.0%) or diabetes mellitus requiring insulin therapy. Concomitant use of the following medications: cyclosporine, itraconazole, ketoconazole, erythromycin, azithromycin, clarithromycin, HIV protease inhibitors, amiodarone, verapamil, telithromycin, digoxin, nefazodone, warfarin, danazol, phenytoin, androgens, cyclic sex hormone therapy or oral contraceptives, oral or systemic use of corticosteroids. Pregnant or lactating women or women of childbearing age who were not using study approved method of contraception. Poorly controlled hypertension (resting BP ≥ 160 mg Hg systolic and/or ≥ 100 mm Hg diastolic at 2 consecutive visits during the lead-in period). Creatine kinase > 2 × upper limits of normal (ULN) at visit 1.

Tests performed: TG, TC, VLDL-C, LDL-C, HDL-C, and apo B levels

Outcome measures: Percent change from baseline to the end of treatment in non–HDL-C. Changes in other lipid parameters (TG, VLDL-C, LDL-C, HDL-C, TC, Apo B) were also assessed as secondary endpoints. Safety profiles were assessed based on adverse events (AEs) recorded at each clinic visit and changes from screening/baseline to the end of treatment in clinical laboratory measurements.

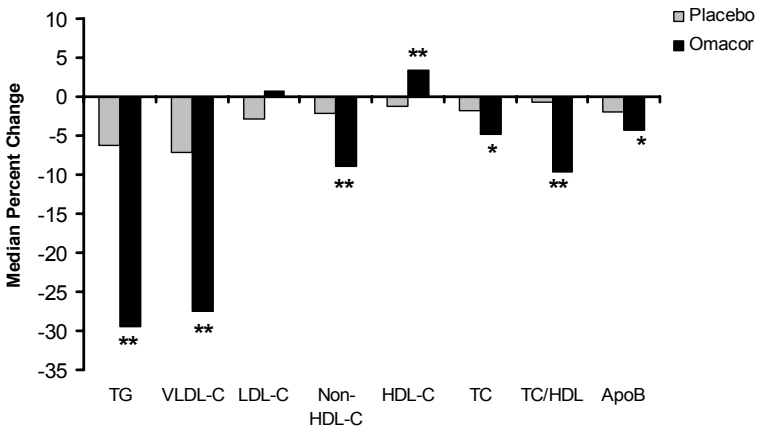
At baseline, no significant differences in lipid-related variables between the Lovaza + simvastatin (n = 122) and placebo + simvastatin (n = 132) groups were noted.

Results: Evaluable population was 254 patients. As shown in Figure 2, 8 weeks of Lovaza™+simvastatin combination treatment resulted in statistically significant reductions compared with placebo+simvastatin in non–HDL-C (-9.0% vs -2.2%; *P* < .001), TG (-29.5% vs -6.3%; *P* = .001), VLDL-C (-27.5% vs -7.2%; *P* < .001), TC (-4.8% vs -1.7%; *P* = .001) and Apo B (-4.2% vs -1.9%; *P* = .02). HDL-C was increased (+3.4% vs -1.2%; *P* < .001) and the TC to HDL-C ratio was reduced (-9.6% vs -0.7%; *P* < .001) in the Lovaza™ + simvastatin subjects, compared with those taking placebo + simvastatin. Prior to randomization, the median baseline levels for LDL-C were low (<91 mg/dL), indicating that patients were controlled for LDL in both treatment arms. The median increase in LDL-C was 0.7% in patients receiving Lovaza™ + simvastatin vs -2.8% in patients receiving placebo + simvastatin; *P* =.0522.

Table 1. Baseline Values in Plasma Lipids

Baseline	TG	VLDL-C	LDL-C	Non–HDL-C	HDL-C	TC	TC/HDL	ApoB (mg/dL)
Placebo + Simvastatin								
mg/dL	270.7	52.0	88.2	141.3	43.3	183.5	4.2	86.8
mmol/L	3.0	1.3	2.3	3.6	1.1	4.7		
Lovaza™ + Simvastatin								
mg/dL	267.8	51.5	90.7	137.0	46.0	184.3	3.9	85.5
mmol/L	3.0	1.3	2.3	3.5	1.2	4.7		

Figure 2. Median Percent Change in Plasma Lipids from Baseline to End of Treatment in the ITT Population



Safety: No significant difference was observed between the two groups in the proportion of subjects who experienced adverse events (Table 1).

Table 2. Incidence of Adverse Events

Adverse Events	Lovaza™ + simvastatin (n = 122)		Placebo + simvastatin† (n = 132)	
	n	%	n	%
Subjects with at least 1 adverse event	51	41.8	63	47.7
Serious adverse events	4	3.3	1	0.8
Specific adverse events*				
Diarrhea	3	2.5	3	2.3
Dyspepsia	3	2.5	3	2.3
Bronchitis	2	1.6	2	1.5
Cystitis	2	1.6	1	0.8
Gastroenteritis	2	1.6	0	0.0
Nasopharyngitis	4	3.3	3	2.3
Upper respiratory tract infection	4	3.3	1	0.8
Alanine aminotransferase increased	2	1.6	1	0.8

*Events reported by ≥1% of patients receiving Lovaza™ + simvastatin that occurred with a higher frequency than in those receiving placebo + simvastatin.

†Placebo was corn oil.

There were no cases of clinically significant increases (>3.0 x ULN) in hepatic transaminase levels (ALT and AST) in either group. There was a slightly higher incidence of mildly elevated ALT in the Lovaza™ + simvastatin group compared with the simvastatin only group (1.6% [2/122] vs 0.8% [1/132]; *P* = 0.61). The group mean changes from baseline in ALT were 5.7 U/L and −0.7 U/L in the Lovaza™ + simvastatin and the simvastatin only groups, respectively (*P* <0.0001). For AST the group mean increases were 1.9 U/L for Lovaza™ + simvastatin and 0.2 U/L for placebo + simvastatin (*P* = 0.0318).

The mean change for fasting glucose (baseline to end of study) was +5.5 mg/dL in the group receiving Lovaza™ + simvastatin and −0.1 mg/dL in the group receiving placebo + simvastatin (*P* =.0022). No adverse events involved myopathy (CK >10 x ULN) or rhabdomyolysis. The combination of Lovaza™ and simvastatin had no significant effect on creatinine, creatine phosphokinase, or homocysteine during the course of the trial.

Serious adverse events

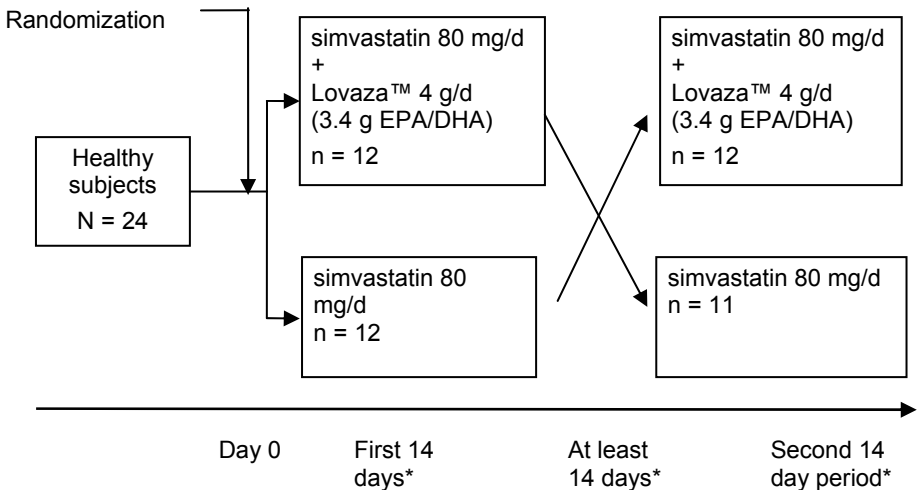
In the Lovaza™ + simvastatin group, 4/122 (3.3%) subjects compared with 1/132 (0.8%) subjects in the placebo group experienced serious adverse events (Table 1). The 4 serious adverse events in the Lovaza™ + simvastatin group included a 68-year-old female hospitalized for an exacerbation of congestive heart failure; a 41-year-old male with a history of hypertension and supraventricular tachycardia hospitalized for supraventricular tachycardia; a 71-year-old female with history of chronic obstructive pulmonary disease hospitalized for pneumonia; and a 54-year-old female with elevated ALT and AST (98 U/L and 68 U/L, respectively). None of these events were considered by the investigators to be related to study treatment.

Conclusion: The authors concluded that the addition of Lovaza™ 4 g/d to ongoing simvastatin 40 mg/day in patients with persistent hypertriglyceridemia was effective in providing additional lowering of non-HDLC, VLDL-C and TG levels.

3.72 McKenney JM, Swearingen D, Di Spirito M, et al. Study of the pharmacokinetic interaction between simvastatin and prescription omega-3-acid ethyl esters. *J Clin Pharmacol.* 2006;46:785-791.[80]

Study Design: McKenney et al conducted an open-label, randomized, 2-way crossover, drug-drug interaction study to evaluate the impact of Lovaza™ on plasma simvastatin single dose and steady state pharmacokinetics. Study design is shown in Figure 1.

Figure 1: Study Design



Blood coagulation parameters were measured at baseline and at the conclusion of each dosing period.

* Simvastatin and β-hydroxy-simvastatin were measured on samples taken prior to dosing on Days 1, 12, 13, and 14 of each 14-day period. Additional samples were collected at the following times after dosing on days 1 and 14: .33, .5, .75, 1, 1.5, 2, 2.75, 3.5, 4.25, 5, 6, 7.5, 9, 11, 13, 16, 20, and 24 hours.

Inclusion criteria: Healthy male or female volunteers, age between18 and 55 years, within 15% of ideal weight according to the 1983 Metropolitan Life Insurance Tables, nonsmokers for at least 3 months before study entry; females were required to be past menopause by more than 2 years, sexually abstinent, or using an acceptable method of birth control.

Exclusion criteria: History of hypersensitivity or idiosyncratic reaction to HMG-CoA reductase inhibitors or lipid-regulating agents, allergy or sensitivity to fish, and use of drugs or substances known to be strong inhibitors or inducers of CYP enzymes within 10 days (inhibitors) or 28 days (inducers) of the first dose.

Concomitant medications: Medications (other than hormonal contraceptives and hormone replacement therapy), herbal products, and vitamins were not to be taken within 7 days of the first dose and during the course of the study. Consumption of substances containing xanthines or caffeine, alcohol, or grapefruit was disallowed 24 hours, 48 hours, or 10 days, respectively, before the first dose and during the course of the study.

Outcome measures: Various pharmacokinetic parameters were calculated with PhAST 2.3-001 software

using noncompartmental methods.

Results: A total of 23 subjects completed the study. One subject who received Lovaza™ with simvastatin during the first dosing period was discontinued from the study during the following washout period because of a serious adverse event. However, data from all 24 subjects (20 male, 4 female) were included in the pharmacokinetic and statistical analyses because all had completed at least one dosing period.

No statistically significant differences in the pharmacokinetic parameters of simvastatin (or β-hydroxy simvastatin, data not shown) were reported on day 1 (single dose) and 14 (steady state) when simvastatin was administered with Lovaza™ compared with when simvastatin was administered alone (Table 3).

Table 1. Lovaza™ Does Not Significantly Affect the Steady-state Pharmacokinetics of Simvastatin

	Day 1			**Day 14**		
	Lovaza™ + Simvastatin N = 24	**Simvastatin N = 23**	***P* Value**	**Lovaza™ + Simvastatin N = 24**	**Simvastatin N = 23**	***P* Value**
AUC_{0-t}, ng.h/mL	121.9 (66.6)	102.4 (73.0)	.204	NC	NC	NC
AUCinf, ng.h/mL	132.4 (72.9)	105.6 (78.1)[a]	.204	NC	NC	NC
AUC_{τ}, ng.h/mL	NC	NC	NC	125.1 (62.9)[b]	116.6 (64.0)[c]	.489
Cmax, ng/mL	20.6 (11.8)	17.1 (9.3)	.131	15.4 (7.6)	13.5 (6.1)	.257
Cavg.ss, ng/mL	NC	NC	NC	5.2 (2.6)[b]	4.9 (2.7)[c]	.489
t_{max}, h	2.1 (2.6)	1.7 (1.5)	.574	2.4 (2.6)	2.6 (1.9)	.775
$t_{½}$, h	6.0 (1.4)	5.6 (1.9)[a]	.523	7.4 (1.6)	9.9 (5.5)	.061
CL/F, L/h	880 (700)	1181 (887)[a]	.052	838 (477)[b]	872 (402)[c]	.619
V_{area}/F, L	7901 (7292)	8978 (6222)[a]	.521	NC	NC	NC
R	NC	NC	NC	1.1 (.5)	1.2 (.7)	.272

Results given as mean (SD).

AUC_{0-t} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; AUC_{inf} = area under the plasma concentration-time curve from zero to infinity; C_{max} = maximum measured plasma concentration; t_{max} = time of the maximum measured plasma concentration; $t_{½}$ = apparent first-order terminal elimination half-life; CL/F = apparent total body clearance after extravascular administration; Varea/F = apparent total volume of distribution after extravascular administration; AUC_{τ} = area under the plasma concentration-time curve over the final 0- to 24-hour dosing interval; Cavg.ss = average concentration over the final dosing interval τ; R = accumulation factor; NC = not calculated.

[a] n = 22; [b] n = 21; [c] n = 18.

No clinically relevant trends were observed in clinical laboratory parameters, blood coagulation (PT, PTT) or platelet aggregation (using ADP and collagen as agonists) variables; vital signs; ECGs; or physical examination findings.

Safety: A total of 32 adverse events occurred in 14 (58%) of 24 subjects. After treatment with Lovaza™ + simvastatin, 18 adverse events were experienced by 9 (38%) of 24 subjects. After treatment with simvastatin alone, 14 adverse events were experienced by 8 (35%) of 23 subjects. One serious adverse event (acute cholecystitis) occurred in a 29-year-old female subject after treatment with Lovaza™ + simvastatin during the washout period. The investigator considered this event unlikely to be related to study drug and the subject was discontinued from the study. All remaining adverse events were mild in severity. Headache, which occurred 4 times, was reported by the greatest number of subjects (3 of 24;

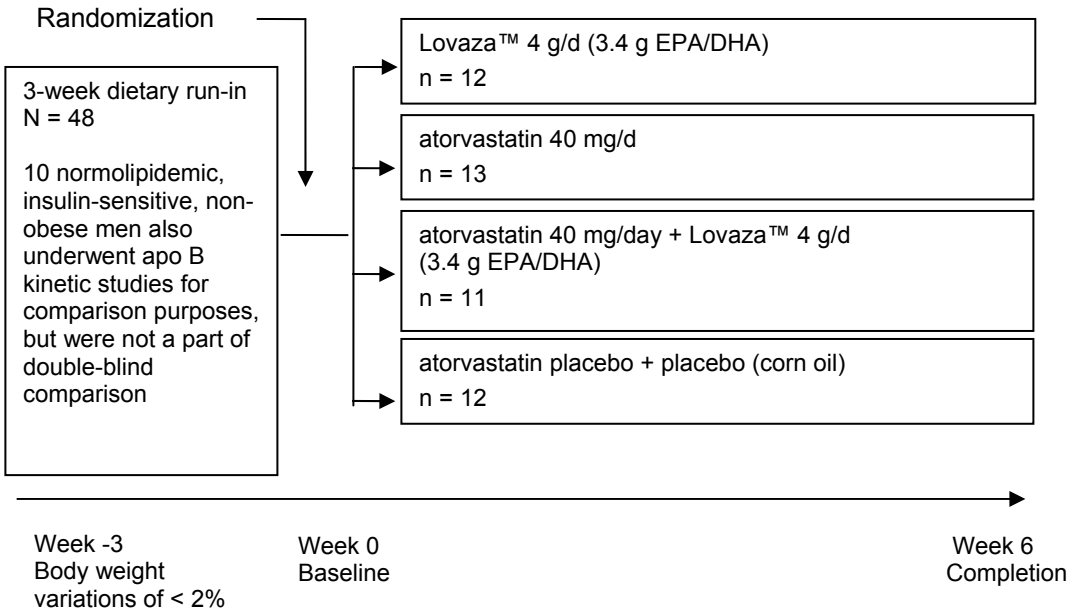
13%). All other adverse events were reported by 2 or fewer subjects (≤8%). Among the adverse events considered possibly related to the study drug included headache (3 of 4 episodes), abdominal distension (1 of 2 episodes), lower abdominal pain (1 of 2 episodes), anorexia (1 episode), constipation (3 episodes), oral hypoesthesia (1 episode), nausea (1 of 2 episodes), generalized pruritus (1 episode), and face swelling (1 episode).

Conclusion: The study concluded that concomitant treatment with Lovaza™ (4g/d) + simvastatin (80 mg) did not significantly affect the steady-state pharmacokinetics of simvastatin.

3.72 Chan DC, Watts GF, Barrett PHR, Beilin LJ, Mori TA. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. *Diabetes* 2002;51:2377-2386.[81]

Study Design: Chan et al performed a randomized, double-bind, placebo-controlled study to evaluate the independent and combined effects of atorvastatin and Lovaza™ on apo-B kinetics in insulin-resistant men with visceral obesity. It was hypothesized that by regulating both hepatic cholesterol and TG availability, atorvastatin and Lovaza™ exert independent and additive effects in improving apo B metabolism in these subjects. Study design is shown in Figure 1.

Figure 1: Study Design



Inclusion criteria: Obese male subjects (waist circumference >100 cm, waist-to-hip ratio >0.97, and a BMI >29 kg/m^2) with insulin resistance (Homeostasis Model Assessment [HOMA] score >5.1) Plasma TG >107 mg/dL (1.2 mmol/L) and TC >203 mg/dL (5.2 mmol/L).

Exclusion criteria: Men with diabetes, apoE2/E2 genotype, macroproteinuria, creatinemia, hypothyroidism, or abnormal liver enzymes.

Tests performed: TG, TC, HDL-C, non–HDL-C, LDL-C RLP-C, apo A-I, apo B, lathosterol, and HOMA scores determined.

Subjects consumed less than one fish meal per week and <30 g alcohol per day and took no fish oils supplements prior to study entry. None reported a history of CVD or was taking agents affecting lipid metabolism.

Outcome measures: Changes in plasma lipid parameters.

Results: This summary will only address overall lipid analyses. For more study detail please refer to the full publication.

Atorvastatin alone significantly decreased plasma TG, TC, non–HDL-C , LDL-C, and apo B as well as increased HDL-C ($P < .01$). There was also a significant main effect of Lovaza™ in lowering plasma TG and raising HDL-C (Table 1). No significant interactions between atorvastatin and Lovaza™ treatment were found for any of the measured variables.

Table 1. Plasma Lipid and Lipoprotein Concentrations in Subjects at Baseline and Post-intervention

	Placebo n = 12	**Atorvastatin n = 13**	**Lovaza™ n = 12**	**Atorvastatin + Lovaza™ n = 11**
TG				
Baseline				
mg/dL†	151.3 ± 16.02	169.1 ± 11.57	178.0 ± 30.26	178.0 ± 18.69
mmol/L	1.7 ± 0.2	1.9 ± 0.1	2.0 ± 0.3	2.0 ± 0.2
Week 6				
mg/dL†	142.4 ± 13.35	124.6 ± 10.68*	133.5 ± 18.69*	106.8 ± 15.13*
mmol/L	1.6 ± 0.2	1.4 ± 0.1	1.5 ± 0.2	1.2 ± 0.2
% change	-5.88	-26.32	-25.00	-40.00
TC				
Baseline				
mg/dL†	226.2 ± 5.46	226.2 ± 6.63	230.1 ± 8.58	245.7 ± 12.48
mmol/L	5.8 ± 0.1	5.8 ± 0.2	5.9 ± 0.2	6.3 ± 0.3
Week 6				
mg/dL†	218.4 ± 5.07	140.4 ± 4.68*	214.5 ± 8.58	152.1 ± 10.53*
mmol/L	5.6 ± 0.1	3.6 ± 0.1	5.5 ± 0.2	3.9 ± 0.3
% change	-3.45	-37.93	-7.00	-38.10
HDL-C				
Baseline				
mg/dL†	40.95 ± 2.34	39.00 ± 1.95	38.61 ± 2.34	42.90 ± 3.51
mmol/dL	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.1 ± 0.1
Week 6				
mg/dL†	40.17 ± 2.34	40.56 ± 1.95	39.00 ± 1.56	48.75 ± 3.51*
mmol/L	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.04	1.25 ± 0.1
% change	-1.90	+4.00	+1.00	+13.64
Non–HDL-C				
Baseline				
mg/dL†	186.03 ± 4.68	187.59 ± 7.02	192.66 ± 8.19	200.85 ± 2.34
mmol/L	4.8 ± 0.1	4.8 ± 0.2	4.9 ± 0.2	5.2 ± 0.1
Week 6				
mg/dL†	178.62 ± 4.29	100.62 ± 4.29*	173.94 ± 9.36	106.08 ± 8.58
mmol/L	4.6 ± 0.1	2.6 ± 0.1	4.5 ± 0.2	2.7 ± 0.2
% change	-3.98	-46.34	-9.72	-47.18
LDL-C				
Baseline				

mg/dL†	148.20 ± 5.07	148.59 ± 6.24	152.88 ± 8.58	157.56 ± 10.92
mmol/L	3.8 ± 0.1	3.8 ± 0.2	3.9 ± 0.2	4.0 ± 0.3
Week 6				
mg/dL†	149.37 ± 4.29	71.76 ± 4.68*	143.52 ± 6.63	83.85 ± 7.41*
mmol/L	3.8 ± 0.1	1.8 ± 0.1	3.7 ± 0.2	2.2 ± 0.2
% change	+.79	-51.71	-6.12	-46.78
Apo B (mg/dL)				
Baseline	129 ± 4	122 ± 6	128 ± 6	134 ± 6
Week 6	123 ± 3	69 ± 3*	118 ± 6	73 ± 5*
% change	-4.65	-43.44	-7.81	-45.52

Data are means + SE. General linear modeling was used to assess the main and interactive effects of atorvastatin and Lovaza™ treatments. No significant interactions between the treatments were noted.
†Data reported in mmol/L were converted to mg/dL: conversion factor—(TG x 89), (TC x 39), (HDL, non–HDL-C, LDL-C x 39).
*P < .05 for t test comparison with placebo group.

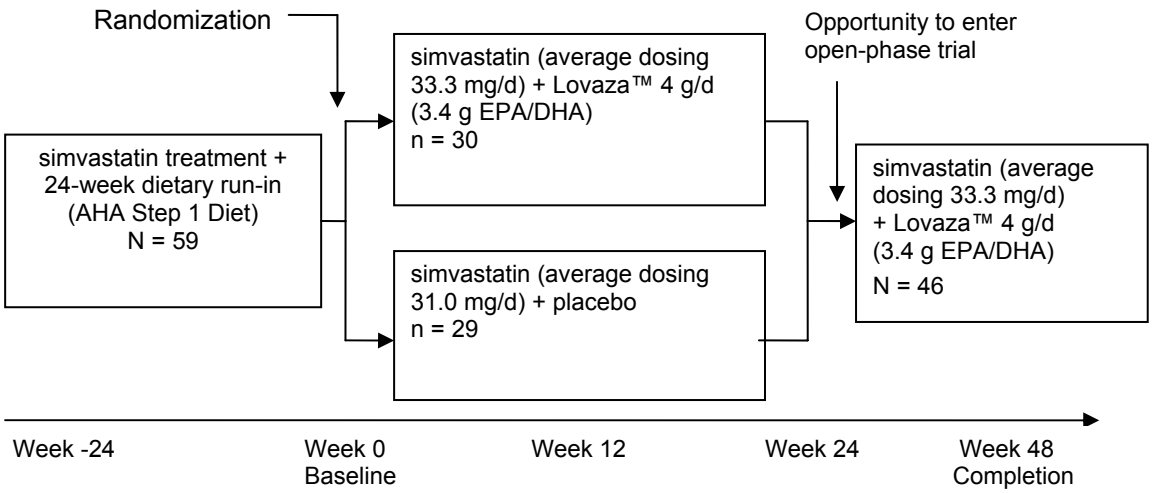
Safety: No adverse events data were reported in the study.

Conclusion: The study concluded that in patients with visceral obesity, treatment with atorvastatin and Lovaza™ significantly improved plasma lipids and lipoproteins levels; however, combination therapy attained the best result in these subjects.

3.73 Durrington PN, Bhatnagar D, Mackness MI, Morgan J, Julier K, Khan MA, France M. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. *Heart* 2001;85:544-548.[82]

Study Design: Durrington et al. conducted a double-blind, placebo-controlled study to measure the efficacy and safety of Lovaza™ in patients with coronary heart disease (CHD) and persistent hypertriglyceridemia despite simvastatin therapy. This study was supported by a grant from Pronova a.s., Norway. Study design is shown in Figure 1.

Figure 1: Study Design



Inclusion criteria: Patients with established CHD with serum TG >205 mg/dL despite simvastatin therapy (10 to 40 mg), which had been unchanged for at least 3 months previously. The simvastatin dose was kept constant throughout the trial. CHD was defined as myocardial infarction (MI) at least 6 months previously with definite ECG and enzyme changes or as angina with a positive exercise ECG. Fifteen patients had type-2 diabetes mellitus.

Exclusion criteria: Patients who had MI within the previous 6 months.

Tests performed: Analysis of serum lipids including TG, TC, VLDL-C, LDL-C, HDL-C, Apo A, and Apo B.

Use of aspirin, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel antagonists, and oral hypoglycemic agents was similar in the placebo and Lovaza™ groups. The 2 treatment groups were similar in most respects at baseline. However, the mean serum TG at randomization was 409 mg/dL in the Lovaza™ group and 338 mg/dL in the placebo group.

Outcome measure: Percentage change in serum TG and VLDL-C. The secondary endpoints were concentrations of serum TC, VLDL-C, and LDL-C.

Results: Of the 55 patients who completed the double-blind, placebo-controlled 24-week phase of the trial, 46 agreed to participate in the 24 week open phase of Lovaza™ treatment.

The addition of Lovaza™ to simvastatin therapy significantly reduced serum TG levels (-23.9%, $P < .0005$) and VLDL-C (-40%, $P < .005$) (Table 1). Results did not change significantly after adjusting for baseline values. At no stage was there any tendency for LDL-C to increase or for HDL-C to decrease.

Table 1. Serum Lipid and Lipoprotein Concentrations in 59 Patients Treated With Simvastatin Randomized to Receive Either Lovaza™ or Placebo

	Simvastatin + Lovaza™			**Open Phase**
				Simvastatin +Lovaza™
Weeks	0 (n = 30)	12 (n = 30)	24 (n = 29)	48 (n =25)
Serum TG				
mg/dL	409.4 ± 195.8	293 ± 124.6[c]	311.5 ± 160.2[c]	267 ± 151.3[c]
mmol/L	4.6 ± 2.2	3.3 ± 1.4	3.5 ± 1.8	3.0 ± 1.7
Serum TC				
mg/dL	218.4 ± 58.5	191.1 ± 46.8[a]	195 ± 46.8 [a]	191.1 ± 35.1
mmol/L	5.6 ± 1.5	4.9 ± 1.2	5.0 ± 1.2	4.9 ± 0.9
VLDL-C				
mg/dL	39 ±19.5	23.4 ± 19.5[b]	23.4 ± 15.6[b]	27.3 ± 19.5[b]
mmol/L	1.0 ± 0.5	0.6 ± 0.5	0.6 ± 0.4	0.7 ± 0.5
LDL-C				
mg/dL	136.5 ± 54.6	120.9 ± 42.9	128.7 ± 46.8	109.2 ± 39[a]
mmol/L	3.5 ± 1.4	3.1 ± 1.1	3.3 ± 1.2	2.8 ± 1.0
HDL-C				
mg/dL	42.9 ± 15.6	46.8 ± 15.6	39 ± 11.7	46.8 ± 15.6
mmol/L	1.1 ± 0.4	1.2 ± 0.4	1.0 ± 0.3	1.2 ± 0.4
	Simvastatin + Placebo			Open Phase
				Simvastatin + Lovaza™
Weeks	0 (n = 29)	12 (n = 27)	24 (n = 26)	48 (n = 21)
Serum TG				
mg/dL	338.2 ± 195.8	347.1 ± 178	347.1 ± 222.5	258.1 ± 169.1[c]
mmol/L	3.8 ± 2.2	3.9 ± 2.0	3.9 ± 2.5	2.9 ± 1.9
Serum TC				
mg/dL	241.8 ± 54.6	245.7 ± 58.5	249.6 ± 58.5	234 ± 54.6
mmol/L	6.2 ± 1.4	6.3 ± 1.5	6.4 ± 1.5	6.0 ± 1.4
VLDL-C				
mg/dL	35.1 ± 23.4	31.2 ± 23.4	31.2 ± 23.4	23.4 ± 23.4[b]
mmol/L	0.9 ± 0.6	0.8 ± 0.6	0.8 ± 0.6	0.6 ± 0.6
LDL-C				
mg/dL	163.8 ± 62.4	163.8 ± 66.3	171.6 ± 66.3	144.3 ± 70.2
mmol/L	4.2 ± 1.6	4.2 ± 1.7	4.4 ± 1.7	3.7 ± 1.8
HDL-C				
mg/dL	42.9 ± 15.6	46.8 ± 19.5	50.7 ± 15.6	50.7 ± 19.5
mmol/L	1.1 ± 0.4	1.2 ± 0.5	1.3 ± 0.4	1.3 ± 0.5

Values are mean ± SD.
[a, b, c]: [a]*P* < .025; [b]*P* < .005; [c] *P*< .0005. Significantly different from baseline values on paired testing
Data reported in mg/dL were converted to mmol/L: conversion factors—(TG⁄89), (TC⁄39), (lipoproteins⁄39).

The changes in serum lipid levels were unrelated to the dose of simvastatin; serum TG levels decreased 25% in patients receiving 10 to 20 mg of simvastatin while similarly, serum TG levels decreased 27% in patients receiving 40 mg of simvastatin.

Safety: Twenty-two patients receiving Lovaza™ and 17 receiving placebo reported adverse events. These events were mostly minor except for 1 patient in the placebo group who died from acute

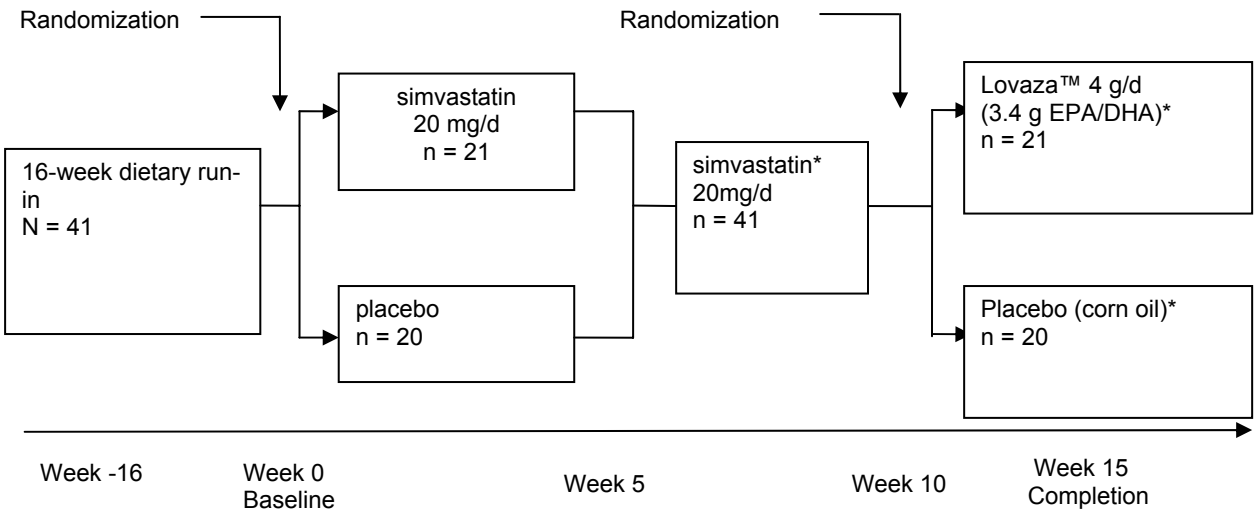
myocardial infarction, for another patient in the placebo group who withdrew because of severe heartburn, and for one patient in the active treatment group who was withdrawn because of diarrhea. Another patient in the placebo group withdrew because visits proved inconvenient. No other safety information is available from the publication.

Conclusion: The study indicated that treatment with Lovaza™ was safe and an effective means of lowering serum TG over 1 year in patients with coronary heart disease and combined hyperlipidemia, whose TG levels remained elevated despite simvastatin treatment.

3.74 Nordoy A, Bønaa KH, Nilsen H, Berge RK, Hansen JB, Ingebretsen OC. Effects of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlidaemia. *J Inter Med*. 1998;243:163-170.[88]

Study Design: Nordoy et al conducted a randomized, double-blind, placebo-controlled, study to measure the efficacy and safety of concomitant treatment with simvastatin and Lovaza™ in patients with combined hyperlipidemia. This study was supported in part by Pharmacia & Upjohn Ltd and MSD Norge AS. Study design is shown in Figure 1.

Figure 1: Study Design



* Each group included an equal number of participants who had received simvastatin for 5 or 10 weeks, respectively.

Inclusion criteria: Fasting serum TC ≥207 mg/dL (5.3 mmolL), and mean serum TG levels between 178 and 1335 mg/dL (2-15 mmolL).

Exclusion criteria: Intake of lipid lowering medications, fish oil, antioxidants, or other medication known to affect lipid metabolism.

Tests Performed: Plasma levels of lipids, lipoproteins, and apolipoproteins

Two patients with prior acute myocardial infarction were without symptoms at the time of study and had diabetes treated with diet only. The others had no cardiovascular, renal, or liver diseases, bleeding disorder, diabetes, alcoholism or other disease that would influence lipid metabolism or haemostasis.

Outcome measures: Changes in fasting lipids from baseline.

Results: This summary will only address overall lipid analyses. For more study detail, please refer to the full publication.

All patients completed the study. Treatment with simvastatin alone reduced serum TC, TG, apo B, apo E from baseline, and increased HDL-C, and apo A-I. Addition of Lovaza™ to simvastatin treatment resulted in further reductions in plasma TG (*P* = .007) and apo-E (*P* = .035) concentrations, whereas HDL-C levels were unaffected (Table 1).

Table 1. Effects of Lovaza™ on Serum Lipids and Lipoproteins in Patients with Combined Hyperlipemia Treated with Simvastatin

	Simvastatin + Lovaza™ n = 21		**Simvastatin + Placebo n = 20**		**Difference between groups**
Variable	Baseline	Change	Baseline	Change	*P**
TG					
mg/dL†	245.64 ± 24.9	-68.53 ± 16.9**	269.67 ± 25.8	41.83 ± 33.8	.007
mmol/L	2.8 ± 0.3	0.8 ± 0.2	3.0 ± 0.3	0.5 ± 0.4	
TC					
mg/dL†	214.5 ± 8.2	-16.38 ± 5.5**	229.71 ± 10.9	5.07 ± 9.4	.052
mmol/L	5.5 ± 0.2	0.4 ± 0.1	5.9 ± 0.3	0.1 ± 0.2	
HDL -C					
mg/dL†	42.51 ± 2.34	1.56 ± 1.17	40.95 ± 2.7	-6.24 ± 3.12	.148
mmol/L	1.1 ± 0.1	0.04 ± 0.03	1.1 ± 0.1	0.2 ± 0.1	
ApoA1 (gL^{-1})	1.42 ± .05	-0.07 ± 0.02*	1.42 ± 0.05	-0.08 ± 0.04	.8
ApoB (gL^{-1})	1.08 ± .05	-0.09 ± 0.03**	1.15 ± 0.05	-0.08 ± 0.03*	.8
ApoE (mgL^{-1})	184 ± 26	-28 ± 13*	228 ± 40	15 ± 15	.035

Values are mean ± SEM.
*P <.05; **P <.01 for significance of change within group.
†Data reported in mmol/L were converted to mg/dL: conversion factors —TG (x89), TC(x39), HDL-C(x39).

Post hoc analysis to evaluate the effect of simvastatin + Lovaza™ therapy on hematostatic risk factors and postprandial hyperlipemia.

Nordoy A, Bønaa KH, Sandset PH, Hansen JB, Nilsen H. Effect of omega-3 fatty acids and simvastatin on hemostatic risk factors and postprandial hyperlipemia in patients with combined hyperlipemia. *Arterioscler Thromb Vasc Biol.*. 2000;20:259-265.[89]

Treatment with Lovaza™ and simvastatin significantly lowered $TFPI_{ag}$ from baseline levels compared with placebo. Combination therapy with Lovaza™ resulted in significant increases in fibrinogen, $FVII_a$, and $PAI\text{-}I_a$ from baseline levels, whereas $FVII_{ag}$ and $TFPI_a$ were decreased; no significant changes were noted

in the placebo group. (Table 2).

Table 2. Effect of Combination Therapy on Hemostatic Factors

	Lovaza™ + simvastatin (n =21)		**Placebo + Simvastatin (n = 20)**	
	Baseline	Change	Baseline	Change
Fibrinogen (g/L)	3.0 ± 0.2	0.4 ± 0.1[a]	3.0 ± 0.2	0.3 ± 0.2
$FVII_{ag}$ (%)	113.0 ± 5.7	-10.0 ± 2.6[b]	120.3 ± 6.1	-8.2 ± 4.3
$FVII_a$ (mU/mL)	68.2 ± 4.6	20.5 ± 5.1[c]	70.7 ± 4.4	8.1 ± 7.5
$TFPI_a$ (U/L)	0.98 ± 0.05	-0.11 ± 0.04[b]	0.92 ± 0.04	-0.09 ± 0.03
$TFPI_{ag}$ (ng/mL)	26.8 ± 1.1	-2.2 ± 0.7[b, d]	25.9 ± 1.7	-0.4 ± 0.6
PAI-1_a (U/mL)	27.8 ± 3.3	5.2 ± 2.3[a]	29.0 ± 2.7	4.4 ± 3.0

[a, b, c] indicate significant difference within group: $P < .05$, $P < .01$, $P < .001$, respectively.
[d]Indicates significant difference between groups, $P < .05$.
$TFPI_a$- lipoprotein bound tissue factor pathway inhibitor activity; $TFPI_{ag}$- lipoprotein free TFPI antigen; $FVII_a$-activated 2-chain form of factor seven; $FVII_{ag}$- factor seven antigen; PAI-1_a-plasminogen activator inhibitor activity.

To evaluate postprandial hypertriglyceridemia, oral fat-load tests were performed at the end of dietary run-in and after the intervention period. Blood samples were drawn in the fasting state and every second hour over an 8-hour postprandial study period. To assess postprandial hypertriglyceridemia, triglyceridemic response (TGR; average of the 2 highest postprandial TG levels minus baseline levels) and the response area under the curve (AUC) of plasma TG were measured.

Combination therapy with Lovaza™ significantly reduced postprandial hyperlipemia, as measured by TG levels (TG AUC), incremental triglyceride levels (TG iAUC) and TGR, compared with placebo. Moderate increase in glucose and a significant rise in insulin levels from baseline were also noted after treatment with Lovaza™ (Table 3).

Table 3. Effect of Combination Therapy on Postprandial Hyperlipedmia and Glucose Metabolism

	Lovaza™ + simvastatin (n = 19)		**Placebo + simvastatin (n = 17)**		
	Baseline	After	Baseline	After	P^d
TG iAUC (mmol/h/L)	14.5 ± 11.7	8.8 ± 4.7[a]	10.7 ± 7.9	15.2 ± 9.6*	0.003
TG AUC (mmol/h/L)	45.9 ± 18.9	23.9 ± 9.1[b]	45.8 ± 33.5	36.8 ± 18.4	0.087
TGR (mmol/L)	3.14 ± 2.12	1.77 ± 0.80[c]	2.20 ± 1.41	2.80 ± 1.56	0.001
Glucose AUC (mmol/h/L)	41.2 ± 3.9	42.3 ± 5.0	44.0 ± 15.4	48.2 ± 10.2	0.312
Insulin AUC (mmol/h/L)	69.9 ± 28.5	92.6 ± 43.8[c]	85.5 ± 29.3	91.5 ± 39.0	0.153
Insulin/glucose ratio	13.5 ± 5.2	17.1 ± 4.9[a]	16.1 ± 6.4	15.3 ± 6.7	0.045

Values are mean ± SD.
TGR=Triglyceridemia response.
[a, b, c] indicates significant difference within group: $P < 0.05$, $P < 0.01$, $P < 0.001$, respectively.
[d]Indicates significant difference between treatment groups.

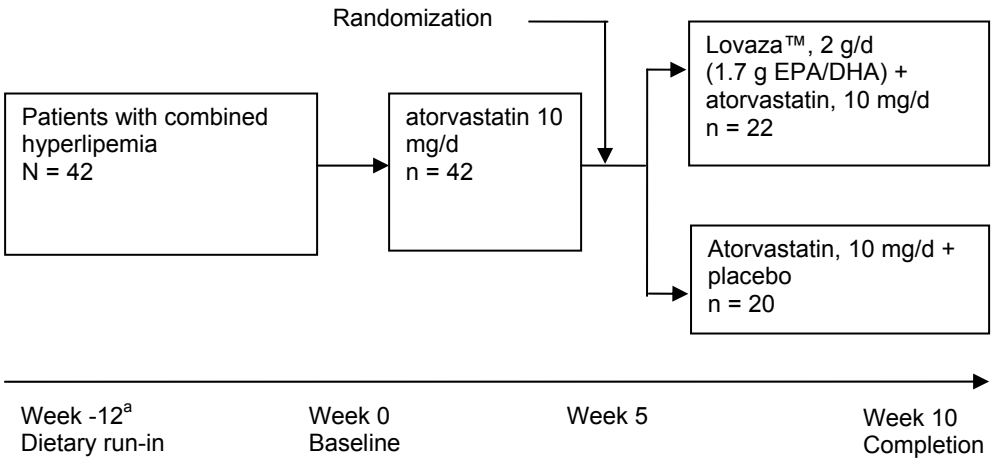
Safety: No adverse events were reported in the publications.

Conclusion: The study concluded that Lovaza™ + simvastatin combination therapy was effective in reducing $TFPI_a$ and $TFIP_{ag}$ in the fasting state and inhibited the activation of $FVII_a$ during postprandial lipemia in patients with combined hyperlipemia.

3.75 Nordoy A, Hansen JB, Brox J, Svensson B. Effects of atorvastatin and omega-3 fatty acids on LDL-C subfractions and postprandial hyperlipemia in patients with combined hyperlipemia. *Nutrition, Metabolism, and Cardiovascular Disease* 2001;11:7-16.[90]

Study Design: Nordoy et al conducted a randomized, double-blind, placebo-controlled, study to assess the efficacy and safety of concomitant treatment with atorvastatin and Lovaza™ in patients with combined hyperlipidemia. This study was supported in part by Pharmacia & Upjohn Ltd and MSD Norge AS. Study design is shown in Figure 1.

Figure 1. Study Design



[a]Patients were advised to adjust their diet, maintain a stable body weight, reduce alcohol intake, and abstain from fish oil supplements. All lipid-lowering medications, fish-oil concentrates, antioxidants, and other medications known to affect lipid metabolism were discontinued.

Inclusion criteria: Patients, aged between 28 and 61 years, with combined hyperlipidemia including those on cholesterol-lowering diet and treated with statins alone or with omega-3 fatty acids supplement. Mean serum TC ≥207 mg/dL (5.3 mmol/L) and mean serum TG between 178 mg/dL (2.0 mmol/L) and 1335 mg/dL (15.0 mmol/L) were required for the intervention.

Exclusion criteria: Cardiovascular, liver or renal diseases; diabetes mellitus; alcoholism or other disorders that affect lipid metabolism.

Tests performed: Serum lipid parameters (TG, TC, lipoproteins, apolipoproteins, total phospholipids), and safety investigations including liver and hematology tests, glucose, HbA_{1c}, uric acid and fibrinogen levels were measured.

Outcome measures: Changes in serum lipid parameters.

Patient characteristics at baseline and after treatment were similar between the treatment groups except for mean systolic blood pressure: 128.8 ± 18.5 mmHg at baseline decreased by -5.5 ± 11.3 mmHg (P < .05) after treatment with Lovaza™, compared with placebo.

Results: All patients completed the study.

Changes in lipid parameters: Treatment with Lovaza™ resulted in a non-significant change in the content

of EPA/ DHA of serum phospholipids.

Atorvastatin alone significantly decreased serum TC (-30%), TG (-25%), LDL-C (-35%), and apoB and apoE (-20%) from baseline levels, whereas HDL-C (8%) and apoA1 (8.5%) levels were increased. Addition of Lovaza™ resulted in a further increase in HDL-C (7%) compared with the placebo group, $P <$. 05 (Table 1). Combination therapy with Lovaza™ plus atorvastatin resulted in a significant redistribution of LDL-C subfractions with a decrease in both LDL_2 and LDL_3 from baseline levels. (Table 2)

Postprandial measurements: To evaluate postprandial hypertriglyceridemia, oral fat load tests were performed at the end of dietary run-in and after the intervention period. Blood samples were drawn in the fasting state and every second hour over an 8-hour postprandial study period. Triglyceridemic response (TGR; average of the 2 highest postprandial TG level minus baseline levels), the area under postprandial curve (AUC), and incremental AUC were measured in plasma and chylomicron. Significant reductions were found in total TG AUCs and iAUCs in both treatment groups; however, TGR was significantly reduced only in Lovaza™ group (Table 3). Lipoprotein lipase (LPL) and hepatic triglyceride lipase (HL) activities were measured before and 15 min after stimulation with 100 IU heparin/kg body weight; both measurements were performed in the fasting state. No significant changes in activity were noted in either treatment group.

Table 1. Effects of Atorvastatin and Lovaza™ Combination Treatment on Serum Lipid Parameters.

	Lovaza™ (n=22)			**Placebo (n=20)**		
	Baseline	atorvastatin	Lovaza™ + atorvastatin	Baseline	atorvastain	Placebo + atorvastain
TC						
mg/dL[d]	300.3 ± 51	-94 ± 36.3 [c]	-2.7 ± 16	325 ± 108	-91.2 ± 83[c]	-14 ± 28.9[a]
mmol/L	7.7 ± 1.3	-2.4 ± 0.9	-0.07 ± 0.4	8.3 ± 2.8	-2.3 ± 2.1	-0.36 ± 0.7
LDL-C						
mg/dL[d]	191.1 ± 66	-74.1 ± 47[c]	-4.7 ± 20	206.2 ± 82	-82 ± 62[c]	-11.7 ± 16[b]
mmol/L	4.9 ± 1.7	-1.9 ± 1.2	0.12 ± 0.5	5.3 ± 2.1	-2.1 ± 1.6	-0.3 ± 0.4
HDL-C						
mg/dL[d]	38.6 ± 8	+3.1 ± 4[c]	+2.7 ± 4[c]	39 ± 12	+5 ± 8[b]	+0.4 ± 4
mmol/L	0.99 ± 0.2	0.08 ± 0.1	0.07 ± 0.1	1.0 ± 0.3	0.13 ± 0.2	0.01 ± 0.1
TG						
mg/dL[d]	338 ± 223	125 ± 134[c]	-3.6 ± 53	374 ± 223	-71 ±187[a]	-27 ± 151
mmol/L	3.8 ± 2.5	-1.4 ± 1.5	-0.04 ± 0.6	4.2 ± 2.5	-0.8 ± 2.1	-0.3 ± 1.7
Apo A-1 (g/L)	1.17	+0.10	+0.05	1.32	0.15[c]	-0.08[a]
Apo B (g/L)	1.25	-0.22[c]	-0.06[a]	1.28	-0.27[c]	-0.05
Apo E (mg/L)	70.5	-24.8[c]	-3.1	75.6	-20.5[c]	-6.0

Values are means ± SD.
[a, b, c] indicate significant difference within group: $P < 0.05$, $P < 0.01$, $P <0.001$, respectively.

[d] Data reported in mmol/L were converted to mg/dL: conversion factors—TCx 39, LDL-C and HDL-C x 39, TG x 89.

Table 2. Effects of Atorvastatin and Lovaza™ Combination Treatment on LDL Subfractions

	Lovaza™ (n = 17)		**Placebo (n = 15)**	
	Baseline	Change	Baseline	Change
LDL	294.6 ± 142.1	-125.4 ± 149.8[b]	256.4 ± 96	-38.7 ± (128.9)[a]
LDL-I	20.8 ± 46	-1.7 ± 53.3	13.3 ± 30.5	-6.2 ± 28.3
LDL-II	147.5 ± 140.5	-76.4 ± 126.5[a]	119.3 ± 106.8	-29.5 ± 141.4
LDL-III	126.3 ± 113.2	-47.4 ± 115.5[a]	123.8 ± 106.9	-2.9 ± 101.9

Values are mean ± SD
[a, b] indicate significant difference within groups: $P < .05$, $P <. 01$, respectively.

Table 3. Effects of Atorvastatin and Lovaza™ Combination Treatment on Postprandial Hypertriglyceridemia.

	Lovaza™ (n=22)		**Placebo (n=20)**	
	Baseline	Change	Baseline	Change
AUC				
Plasma TG (mmol/L/h)	47.6 ± 30.1	-17.2 ±16.5[c]	49.3 ± 21.7	-10.8 ±14.9[b]
Chylomicron TG (µmol/L/h)	1084.3 ± 797.3	-357.9 ± 527.2 [c]	1171.0 ± 568.3	-238.8 ± 413.5[a]
iAUC				
Plasma TG (mmol/L/h)	16.5 ± 12.9	- 7.0 ± 12.6[a]	13.7 ± 7.8	-1.2 ± 15.4
Chylomicron TG (µmol/L/h)	878.5 ± 686.4	-347.0 ± 494.6[b]	871.8 ± 465.9	-186.4 ± 626.5[a]
TGR				
Plasma TG (mmol/L/h)	3.13 ± 2.28	-1.22 ± 2.03 [b]	2.84 ±1.34	-0.35 ± 2.34
Chylomicron TG (µmol/L/h)	168.3 ± 124.0	-58.7 ± 95.5 [b]	170.7 ± 80.7	-30.0 ± 110.7

Values are mean ± SD.
[a, b, c] indicate significant difference within groups: $P < 0.05$, $P <0.01$, $P <0.001$, respectively.

Safety

No side effects were reported in the publication. Body weight remained unchanged and no significant changes were noted in serum ALT, γ-glutamyltransferase, or creatinine kinase.

Conclusion: The authors concluded that addition of a low dose of Lovaza™ may further improve the risk profile for CHD in patients with combined hyperlipemia treated with atorvastatin. The authors noted the effect might be related to a reduction in postprandial hyperlipemia and to redistribution of LDL-C subfractions.

4.0 Summary Spreadsheet

4.1 Pivotal Safety and Efficacy Studies: Lovaza™ 4 g/day Monotherapy for Treatment of Very High Hypertriglyceridemia (TG ≥500 mg/dL)

Safety and Efficacy

Citation	Design/ Duration	Treatment	Inclusion & exclusion Sample size	Outcome measurements	Results	Conclusion Safety
Harris et al[78] Safety and efficacy of Omacor in severe hypertriglyceridemia. *Journal of Cardiovascular Risk* 1997;4 (5-6): 385-391.	16-week, randomized, double-blind, placebo-controlled study.	Lovaza 4g/day Vs. Placebo (corn oil)	Inclusion: Patients aged between 18 and 75 yrs with mean TG ≥ 500 mg/dL (5.6 mmol/L) and < 2000 mg/dL (22.5 mmol/L) Exclusion: type III hyperlipidemia, MI < 6 mos prior, serum ALT >3x ULN, fasting serum glucose > 200 mg/dL (11.1 mmol/L), serum creatinine > 2 mg/dL, platelet counts <60 x 10^9/l, hemoglobin M 10 g/dL, clinically significant disease; females pregnant or breastfeeding, excessive ETOH (> 2 per day), abused drugs or compliance risks Sample size: 42	Change in TG, VLDL-C, LDL-C, and HDL-C levels from baseline to endpoint.	Treatment with Lovaza significantly reduced serum TG (-45%, $P < 0.0001$) and VLDL-C (-43.4%, $P < 0.0001$) levels from baseline compared with placebo, whereas LDL-C and HDL-C levels were raised by 31.6% ($P = 0.0014$) and 13.3% ($P = 0.014$) from baseline respectively, compared with placebo.	Safety: Gastrointestinal side effects occurred in both treatment groups. None of the treatment-related side effects were serious, and side effects did not lead to discontinuation of treatment in any of the patients. Conclusion: The study concluded that treatment with Lovaza significantly decreased the levels of serum TG in patients with hypertriglyceridemia. The authors also noted that treatment with Lovaza may reduce the risk of developing acute pancreatitis and diminish the long-term risk of CVD in patients with hypertriglyceridemia.

Pownall et al[79] Correlation of serum triglyceride and its reduction by omega-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins. *Atherosclerosis* 1999;143: 285-297.	6-week, randomized, double-blind, placebo-controlled study.	Lovaza 4 g/day vs Placebo (corn oil)	Inclusion: Patients, between 18 and 70 yrs with mean fasting TG > 500 mg/dL (5.6 mmol/L) and < 2000 mg/dL (22.5 mmol/L) despite dietary counseling. Exclusion: fibrate <3 months; another omega-3 fatty acid, cod-liver oil or dietary fiber with lipid-lowering effects < 4 weeks prior; cold-water fish > 1x/wk; MI or serious disease prior 6 mos; serum ALT >3x ULN; serum glucose > 300 mg/dL (16.7 mmol/L), serum creatinine > 176.9 umol/l; platelet <60 x 109/l, hemoglobin <100 g/dL; pregnant or breastfeeding, ETOH or drug abuse, and type 1 diabetes mellitus.	Change in fasting TG, VLDL-C, LDL-C, and HDL-C from baseline to endpoint.	Treatment with Lovaza significantly reduced TG (-38.9%, *P* < 0.0001) and VLDL-C (-29%, *P* = .001) levels from baseline compared with placebo; whereas, LDL-C and HDL-C levels were raised by 16.7% (*P* = .007) and by 5.9% (P = .057) from baseline respectively, relative to placebo.	Safety: No serious side effects were reported. Conclusion: The primary clinical objective of the study was to determine the effects of Lovaza on serum TG levels and on other lipid variables. Treatment with Lovaza significantly lowered serum TG, TC and VLDL-C and increased HDL-C and LDL-C levels from baseline in patients with hypertriglyceridemia.

4.2 Safety and Efficacy Studies: Lovaza™ Monotherapy at 4 g/day for Treatment of Very High and High Hypertriglyceridemia (TG >200mg/dL or 2.25 mmol/L)

Safety and Efficacy

Borthwick L.[82] The effects of an omega-3 ethyl ester concentrate on blood lipid concentrations in patients with hyperlipidaemia. *Clinical Pharmacodynamics.* 1998; 15: 397-404.	12-week, randomized, double-blind, placebo-controlled study.	Lovaza 4 g/day vs Placebo	Inclusion criteria: Patients, aged 18 to 70 years, with hyperlipidemia, mean fasting TG levels between 178 mg/dL (2 mmol/L) and 890 mg/dL (10 mmol/L), and TC ≥203 mg/dL (5.2 mmol/L), a change in body weight during the run-in period of less than 1 kg/week. Exclusion criteria: not stated in the study. Sample size: 55	Changes in serum lipid parameters.	Treatment with Lovaza reduced plasma TG levels from baseline compared with a non-significant increase in the placebo group. No significant changes were found in other lipid parameters between or within treatment groups. No significant changes in serum TC, HDL-C were observed in either treatment group.	Safety: Gastrointestinal effects including nausea, indigestion, and diarrhea were the most prevalent adverse effects, while influenza, sore throat, rash, chest infection, and headache were also reported. Conclusion: The study concluded that administration of Lovaza 4 g/day to patients with hyperlipidemia was sufficient to achieve a substantial TG-lowering effect (-28%) compared with a non-significant increase in the placebo group.

Mackness et al. [83] Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridaemia. *European J Clinical Nutrition* 1994;48:859-865.	14-week, randomized, double-blind, placebo-controlled study.	Lovaza 4 g/day vs Placebo (corn oil)	Inclusion: Patients, aged 18 to 70 years, with primary type IIb or type IV hyperlipidemia: fasting serum TG 178 mg/dL (2 mmol/L) - 890 mg/dL (10 mmol/L), TC> 203 mg/dL (5.2 mmol/L). Exclusion criteria: diabetes mellitus, hypothyroidism, serious illness in the previous 3 months, including myocardial infarction, or severe concurrent illness.. Sample size: 79	Changes in serum levels of TG and cholesterol, VLDL, LDL-C, HDL-C, fasting blood glucose, and blood pressure.	Treatment with Lovaza significantly reduced serum Levels of TG and VLDL-C from baseline; however, the concentrations of serum TC, LDL-C, and HDL-C did not change significantly. In a secondary analysis, patients were subdivided into 2 groups; one with an LDL-C concentration >176 mg/dL (>4.5 mmol/L, Type IIb hyperlipidemia) and the other with an LDL-C <176 mg/dL (<4.5 mmol/L, Type IV hyperlipidemia). After 14 weeks of treatment with Lovaza, serum TG and VLDL-C were reduced significantly from baseline in patients with Type IIb hyperlipidemia	Safety: Diastolic blood pressure decreased from a baseline level of 86 ± 11 mm Hg to 80 ± 12 mm Hg (P < .02) after treatment with Lovaza, which was also lower than in the placebo group (84 ± 12 mm Hg to 82 ± 10 mm Hg, P < .05). Conclusion: The study concluded that Lovaza was effective in lowering serum TG and VLDL-C levels in patients with primary hypertriglyceridemia and may be used as a TG-lowering agent.
Stalenhoef et al. [84] The effect of concentrated n-3 fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidazability in patients with hypertrygliceridemia. *Atherosclerosis* 2000; 153: 129-138.	12-week, randomized, double-blind, double-dummy study.	Lovaza 4 g/day + Gemfibrozil placebo vs Gemfibrozil 1200 mg/day + Lovaza placebo.	Inclusion criteria*: P*rimary hypertriglyceridemia (plasma TG levels 356 mg/dL (4 mmol/L) - 2492 mg/dL (28 mmol/L). Exclusion criteria: Secondary causes of dyslipidemia, including history of diabetes mellitus, or apolipoprotein phenotype E2/E2. Sample size: 28	To compare the effects of Lovaza vs gemfibrozil on LDL heterogeneity in patients with hypertriglyceridemia	Treatment with gemfibrozil and Lovaza significantly decreased the levels of plasma lipids and lipoproteins from baseline; the differences were not significant between the treatment groups Significant increases were found in the cholesterol content of LDL-C_1, LDL-C_2 and LDL-C_3 from baseline, resulting in a more buoyant LDL subfraction profile after treatment with Lovaza and gemfibrozil.	Safety: no significant adverse events were reported. Conclusion: The authors concluded that both Lovaza and gemfibrozil have favorable anti-atherogenic properties on lipid and lipoprotein levels and LDL subfraction profile.

Westphal et al.[67] Postprandial chylomicrons and VLDLs in severe hypertriacylglycerolemia are lowered more effectively than are chylomicron remnants after treatment with n-3 fatty acids. *Am J Clin Nurt* 2000;71:914-20.	6-week, open-label study.	Lovaza 4 g/day	Inclusion criteria: Patients (mean age of 46 ± 6 years and BMI of 27.7 ± 7kg/m^2) with hypertriglyceridemia were recruited; fasting TG levels >300 mg/dL (3.4 mmol/L). Exclusion criteria: Age >65 years, Type III hyperlipoproteinemia, thyroid dysfunction, fasting blood glucose >140 mg/dL (7.8 mmol/L), alcohol abuse (> 2 drinks/d), serum creatinine >2.0 mg/dL (176.8 μmol/L), serum ALT >3 x upperlimit of the normal range, consumption of fish meals >1 time/week, and treatment with lipid-lowering agents or omega-3 supplements prior to 2 months of enrollment. Sample size: 12	Changes in serum lipids including chylomicron remnants from baseline to study end.	In the fasting state, treatment with Lovaza significantly lowered VLDL-TG (-44%), VLDL-C (-40%), TC (-14%) and increased LDL-C (+45%) from baseline (before treatment) levels. No significant difference was noted in the levels of HDL-C or lipoprotein lipase. In the postprandial state, chylomicron-TG levels decreased by 49%, 58%, and 64% at 4, 6, and 8 h, respectively (P <.05), compared with before treatment. Chylomicron remants were reduced only in the late postprandial phase: at 8 h, large remants were significantly decreased by -43% (P <.05) and small remnants by -31% (P <.05), compared with before treatment levels.	Safety**:** No adverse events were reported. Conclusion: The study concluded that treatment with Lovaza effectively lowered chylomicrons and VLDLs; however the lowering effect of chylomicron remnants was observed only in late postprandial phase.
4.3 Lovaza™ Monotherapy at Doses of 4 g/d: Patients with Familial Combined Hyperlipidemia Safety and Efficacy						
Calabresi et al[63] in familial combined hyperlipidemia: effects of lipids and low density lipoprotein subclasses. *Atherosclerosis* 2000;148: 387-96.	16-week, randomized, double-blind, placebo-controlled, crossover study.	Weeks 0-8 Lovaza 4 g/day vs Placebo, Week 8-16 reverse treatment.	Inclusion criteria*:* Patients with FCHL: TC and/or TG exceeding the 90th percentile in the general population adjusted for age and sex. Presence of hyperlipidemia for at least 1 year with LDL phenotype B as defined by a major LDL particle subpopulation with a diameter <25.5 nm. At least one first-degree relative diagnosed with hyperlipidemia different from the subject. Exclusion criteria: Patients with a plasma Lp(a) concentration > 30 mg/dL. Sample size: 14	Changes in lipid and lipoprotein parameters, and LDL subclass distribution.	Treatment with Lovaza significantly reduced plasma TG and VLDL-C levels from baseline (-27% and -18%, respectively, whereas LDL-C was increased by 25% relative to placebo. Treatment with Lovaza significantly altered LDL composition and subclass distribution: plasma levels of IDL, LDL_1 and LDL_2 were increased with a concomitant decrease in LDL_3 levels compared with baseline and placebo measurements. No significant changes were noted in the mean diameter of LDL size after treatment with Lovaza or placebo (25 ± 0.3 nm and 24.8 ± 0.5 nm, respectively).	Safety*:* No drug-related adverse events were reported. Conclusion**:** the study concluded that Lovaza effectively lowered plasma TG and VLDL levels in patients with FCHL, and redistributed LDL subfractions from dense to buoyant LDL particles; however, the size of LDL particles was not affected by treatment, suggesting that the LDL size in FCHL was independent of plasma lipid/lipoprotein levels.

4.4 Lovaza™ 4 g/d Monotherapy: Patients with Combined Hyperlipidemia

Safety and Efficacy

Grundt et al[85] Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlidaemia. *J Intern Med* 1995;237: 249-59.	12-week, randomized, double-blind, placebo-controlled study	Lovaza 4 g/day vs Placebo (corn oil)	Inclusion criteria**:** Patients, aged 18 to 70 years, with combined hyperlipidemia and mean change in body weight of less than 1 kg/week during the dietary run-in period; serum TG levels 178 mg/dL - 1335 mg/dL; and TC ≥6 mmol/L (234 mg/dL). Exclusion criteria: Use of dietary supplement, medication containing omega-3 fatty acids, or antihyperlipemic medication during the run-in period; myocardial infarction or other serious illness in the preceding 3 months of trial entry; diabetes mellitus, serious psychological illness, known drug or alcohol abuse, pregnancy, and lactation as well as clinically significant biochemical anomalies based on laboratory tests. Sample size: 56	Changes in serum lipids and lipoprotein levels.	Treatment with Lovaza significantly reduced TG levels by 28% from baseline, reaching statistical significance as early as 4 weeks after treatment initiation ($p<0.05$). A decrease in serum TC and an increase in HDL-C levels were observed in both treatment groups.	Safety: Side effects were all mild and mainly involved gastrointestinal complaints. Patients in the Lovaza group showed a significant decrease in both systolic and diastolic blood pressure and heart rate during the 12-week intervention period. No significant changes in blood pressure were noted in the placebo group. Conclusion: the study concluded that 12 weeks of treatment with Lovaza 4 g/day significantly reduced serum lipids, blood pressure, and heart rate in patients with combined hyperlipidemia and thereby improved the atherogenic risk profile in these patients.

4.5 Lovaza™ Monotherapy: Secondary Prevention Post Myocardial Infarction

Safety and Efficacy

GISSI-Prevenzione Investigators.[10] Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin e after myocardial infarction: Results of the GISSI-Prevenzione trial. *Lancet* 1999;354: 447-55.	3-5 year, randomized, open-label study.	Control vs Lovaza 1 g/day vs Vitamin E 300 mg/d vs Lovaza 1 g/day + Vitamin E 300 mg/d	Inclusion criteria: Patients with recent (<3 months) MI, who were able to provide informed written consent. Exclusion criteria: Known congenital defects of coagulation, known allergy or contraindications to Lovaza or vitamin E, unfavorable short-term outlook (congestive heart failure, cancer etc). Sample size: 11,324	Primary combined efficacy endpoints were cumulative rate of all-cause death, non-fatal MI, and non-fatal stroke; and cumulative rate of cardiovascular death, non-fatal MI, and non-fatal stroke.	Treatment with Lovaza resulted in a small but significant decrease (-3.4%) in TG levels, compared with the control group. No significant changes were noted in other blood lipid levels compared with baseline values. Treatment with Lovaza significantly lowered the risk of combined primary endpoint of death, non-fatal MI, and non-fatal stroke by 15% compared with the control group (P = .023, 4-way factorial analysis); the relative decrease in risk for cardiovascular death, non-fatal MI and non-fatal stroke was 20% (P=.008) compared with the control group. No added benefit was apparent with the combined treatment	Safety: Gastrointestinal disturbances and nausea were the most frequently reported side-effects (4.9% and 1.4%, respectively in Lovaza group; 2.9% and 0.4%, respectively in vitamin E group). Cancer was reported with equal prevalence in all treatment groups. Conclusion: the study concluded that treatment with Lovaza 1 g/day resulted in a clinically important and statistically significant benefit, whereas vitamin E had no benefit.
Nilsen DWT, Albrelasen G, Landmark K, Moen S, Aarsland T, Woie L.[86] Effects of a high-dose concentration of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001;74: 50-6.	12- to 24-month, randomized, double-blind, placebo-controlled study.	Lovaza 4 g/day vs Placebo]	Inclusion criteria**:** Patients, aged 18 years and above, with a history of acute MI verified by WHO criteria Exclusion criteria*:* Non-compliance to protocol, life expectancy <2 years because of heart failure, malignancy or other reasons, gastrointestinal bleeding and/or stomach ulcer, blood platelets 100 × 109/L, liver insuffciency, involvement in another study and residence outside the recruitment area Sample size: 300	Changes in serum lipid levels and cardiac event rates	Treatment with Lovaza significantly reduced serum TG levels and increased HDL-C levels from baseline compared with placebo measurements. Twenty-eight percent of patients in the Lovaza group and 24% in the placebo group experienced at least 1 cardiac event during the follow-up period (hazard ratio between Lovaza and placebo groups: 1.19); cardiac events were defined as death, resuscitation, recurrent MI, and unstable angina. However, no significant difference was found between the groups in number, type, or severity of the event	Safety**:** Forty-two patients in the Lovaza group and 36 patients in the placebo group experienced at least 1 cardiac event; unstable angina was the most common type among the predefined cardiac events followed by recurrent MI. Conclusion**:** the study concluded that treatment with Lovaza significantly reduced serum TG and increased HDL-C levels from baseline compared with placebo; however, administration of Lovaza early after an acute MI had no significant benefit compared with placebo.

4.6 Lovaza™ Monotherapy at Doses Exceeding 4 g/d: Additional Safety and Efficacy Studies in Healthy Subjects Safety and Efficacy						
Bonaa KH, Bjerve KS, Nordoy A.[87] Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. *Arteriosclerosis* and Thrombosis 1992;12: 675-681.[107]	10-week randomized, double-blind, placebo-controlled study.	Lovaza 6 g/day vs Placebo (corn oil)	Inclusion criteria: Patients, aged 34 to 60 years, with untreated, stable essential hypertension were included; patients were not previously treated with lipid-lowering or antihypertensive drugs. All patients had serum TC levels between 203 mg/dL (5.2 mmol/L) and 390 mg/dL (10.0 mmol/L); mean diastolic blood pressure between 85 and 110 mmHG; mean systolic blood pressure below 180 mmHg. Clinical examination, laboratory tests and ECG were performed to determine the health of the patients. Exclusion criteria: Cardiovascular disease, bleeding disorder, diabetes mellitus, disabling chronic disease, psychopathologic disease, alcoholism, obesity (BMI >32) Sample size: 146	Changes in serum lipid parameters.	Treatment with Lovaza significantly reduced plasma TG levels from baseline compared with no change in the placebo group. The decrease in serum TG levels correlated significantly with the increase in EPA and DHA levels: EPA (r = -0.3, *P* < .05), DHA (r= -0.27, *P* < .05). Significant increases were also noted in HDL-C levels after Lovaza treatment, which correlated significantly with the change in plasma EPA levels (r = 0.33, *P* = .006); in the placebo group, an inverse correlation was found between the change in serum HDL-C and plasma DHA levels.	Safety: Mild to moderate abdominal discomfort was reported by 10 patients in the Lovaza group and 7 patients in the placebo group. Conclusion: the study indicated that treatment with Lovaza resulted in differences in the content of EPA and DHA that correlated significantly in relation to both HDL-C and apo A-1 levels.

4.7 Lovaza™ Combination Therapy with Statins

Safety and Efficacy

Davidson MH, Stein EA, Bays HE, et al.[18] Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther* 2007; 29(8): 1-14.[81]	8-week multicenter, randomized, double-blind, placebo-controlled study.	Lovaza 4 g/d + Simvastatin 40 mg/d vs Pla + Simvastatin 40 mg/d	Inclusion criteria: Patients, aged 18 to 79 years, on statin therapy who were at or within 10% of their NCEP ATP III LDL-C goals during the lead-in with persistent hypertriglyceridemia (TG 200 to 499 mg/dL; 2.2 to 5.6 mmol/L). Exclusion criteria: Use of any non–study-related lipid-altering drugs or omega-3 fatty acids supplements. History of cardiovascular event (i.e. myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, unstable congestive heart failure requiring a change in treatment) or revascularization procedure in the 6 months prior to enrollment. Poorly controlled diabetes mellitus (HbA1C > 8.0%) or diabetes mellitus requiring insulin therapy. Concomitant use of the following medications: cyclosporine, itraconazole, ketoconazole, erythromycin, azithromycin, clarithromycin, HIV protease inhibitors, amiodarone, verapamil, telithromycin, digoxin, nefazodone, warfarin, danazol, phenytoin, androgens, cyclic sex hormone therapy or oral contraceptives, oral or systemic use of corticosteroids. Pregnant or lactating women. Poorly controlled hypertension. Creatine kinase > 2 × upper limits of normal (ULN) at visit 1. Sample size: 254.	Percent change in non-HDL-C, TG, VLDL-C, LDL-C, HDL-C, TC, and apo B from baseline to end of study.	Lovaza+ simvastatin combination treatment resulted in significant reductions compared with placebo+simvastatin in non–HDL-C (-9.0% vs -2.2%; *P* < .0001), TG (-29.5% vs -6.3%; *P* = .0001), VLDL-C (-27.5% vs -7.2%; *P* < .0001), TC (-4.8% vs -1.7%; *P* = .001) and Apo B (-4.2% vs -1.9%; *P* = .02). HDL-C was increased (+3.4% vs -1.2%; *P* < .0001) and the TC to HDL-C ratio was reduced (-9.6% vs -0.7%; *P* < .0001) in the Lovaza + simvastatin patients, compared with those treated with placebo + simvastatin.	Safety: No significant difference was observed between the two groups in the proportion of subjects who experienced adverse events. Conclusion: The authors concluded that the addition of Lovaza 4 g/day to ongoing simvastatin 40 mg/day in patients with persistent hypertriglyceridemia was effective in providing additional lowering of non-HDLC, VLDL-C and TG levels.

McKenney JM, Swearingen D, Di Spirito M, et al. [80] Study of the pharmacokinetic interaction between simvastatin and prescription omega-3-acid ethyl esters. *J Clin Pharmacol*; 2006;46: 785-791.[99]	6-week, randomized, open-label, 2-way crossover, drug-drug interaction study.	Patients were randomized to receive Lovaza 4 g/day + Simvastatin 80 mg/day vs Simvastatin 80 mg/day alone for 14 days followed by a 14-day washout period and then the alternate treatment	Inclusion criteria: Healthy volunteers, aged 18 to 55 years, within 15% of ideal weight according to the 1983 Metropolitan Life Insurance Tables, nonsmokers for at least 3 months before study entry; females were required to be past menopause by more than 2 years, sexually abstinent, or using an acceptable method of birth control. Exclusion criteria: History of hypersensitivity or idiosyncratic reaction to HMG-CoA reductase inhibitors or lipid-regulating agents, allergy or sensitivity to fish, and use of drugs or substances known to be strong inhibitors or inducers of CYP enzymes within 10 days (inhibitors) or 28 days (inducers) of the first dose. Sample size: 23	Area under the plasma concentration-time curve over the final 0-to-24-hour dosing interval (AUC_T) and the maximum plasma concentration over the final dosing interval (Cmax) on day 14.	No statistically significant differences in the pharmacokinetic parameters of simvastatin (or β-hydroxy simvastatin) were observed when simvastatin was administered alone or with Lovaza.	Safety: Adverse events were mild in severity. Among the adverse events considered possibly related to the study drug included headache (3 of 4 episodes), abdominal distension (1 of 2 episodes), lower abdominal pain (1 of 2 episodes), anorexia (1 episode), constipation (3 episodes), oral hypoesthesia (1 episode), nausea (1 of 2 episodes), generalized pruritus (1 episode), and face swelling (1 episode). Conclusion: The study concluded that concomitant treatment with Lovaza (4g/day) + simvastatin (80 mg) did not significantly affect the steady-state pharmacokinetics of simvastatin.
Chan DC, Watts GF, Barrett PHR, Beilin LJ,[81] Redgrave triglycerides, Mori TA. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. *Diabetes* 2002; 51:2377-2386.	6-week, randomized, double-blind, placebo-controlled study.	Atorvastatin 40 mg/day vs Lovaza 4g/day vs Atorvastatin 40 mg/day + Lovaza 4g/day vs placebo Atorvastatin + placebo Lovaza	Inclusion criteria**:** Obese male subjects (waist circumference >100 cm, waist-to-hip ratio >0.97, and a BMI >29 kg/m^2) with insulin resistance (Homeostasis Model Assessment [HOMA] score >5.1) Plasma TG >107 mg/dL (1.2 mmol/L) and TC >203 mg/dL (5.2 mmol/L) Exclusion criteria**:** Men with diabetes, apoE2/E2 genotype, macroproteinuria, creatinemia, hypothyroidism, or abnormal liver enzymes. Sample size: 48	Changes in plasma lipid parameters.	Atorvastatin alone significantly decreased plasma TG, TC, non–HDL-C , LDL-C, and apo B and increased HDL-C from baseline levels ($P < .01$). There was also a significant main effect of Lovaza in lowering plasma TG and raising HDL-C. No significant interactions between atorvastatin and Lovaza treatment were found for any of the measured variables.	Safety: No adverse events data were reported in the study. Conclusion: The study concluded that in patients with visceral obesity treatment with atorvastatin and Lovaza significantly improved plasma lipids and lipoproteins levels; however, combination therapy attained the best result in these subjects.

Durrington PN, Bhatnagar D, Mackness MI, Morgan J, Julier K, Khan MA, France M.[82] An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. *Heart* 2001;85: 544-548.[82]	2-phase study: Phase 1: 24-weekk, randomized, double-blind Phase 2: 24-week open-label study	Phase 1: Simvastatin + Lovaza 4 g/day vs Simvastatin + Placebo Phase 2: Simvastatin + Lovaza 4 g/day	Inclusion criteria: Patients with established CHD with serum TG >205 mg/dL (2.3 mmol/L) despite simvastatin therapy (10 to 40 mg), which had been unchanged for at least 3 months previously. The simvastatin dose was kept constant throughout the trial. CHD was defined as myocardial infarction (MI) at least 6 months previously with definite ECG and enzyme changes or as angina with a positive exercise ECG. Exclusion criteria**:** Patients who had MI within the previous 6 months. Sample size: 46	Percentage change in serum lipids and lipoproteins	The addition of Lovaza to simvastatin therapy significantly reduced serum TG levels (-23.9%, *P* < .0005) and VLDL-C levels (-40%, *P* < .005). Results did not change significantly after adjusting for baseline values. At no stage was there any tendency for LDL-C to increase or for HDL-C to decrease. The changes in serum lipid levels were unrelated to the dose of simvastatin; serum TG levels decreased 25% in patients receiving 10 to 20 mg of simvastatin while similarly, serum TG levels decreased 27% in patients receiving 40 mg of simvastatin.	Safety: The adverse events were mostly minor except for 1 patient in the placebo group who died from acute MI, and another patient in the placebo group withdrew because of severe heartburn. Conclusion: The study indicated that treatment with Lovaza was safe and effective means of lowering serum TG over 1 year in patients with coronary heart disease and combined hyperlipidemia, whose TG levels remained elevated despite simvastatin treatment.

Nordoy A, Bonaa KH, Nilsen H, Berge RK, Hansen JB, Ingebretsen OC.[88] Effects of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlidaemia. *J Inter Medicine* 1998;243: 163-170. Post hoc analysis to evaluate the effect of simvastatin + Lovaza combination therapy on hemostatic risk factors: Nordoy A, Bønaa KH, Sandset PH, Hansen JB, Nilsen H.[89] Effect of omega-3 fatty acids and simvastatin on hemostatic risk factors and postprandial hyperlipemia in patients with combined hyperlipemia. *Arterioscler Thromb Vasc Biol.*. 2000;20:259-265.[111]	15-week, randomized, double-blind, placebo-controlled study.	Simvastatin 20 mg/day vs Placebo for 5 weeks followed by All patients: Simvastatin 20 mg/day for 5 wks followed by Simvastatin 20 mg/day + Lovaza 4 g/day vs Simvastatin 20 mg/day + Placebo for 5 weeks	Inclusion criteria**:** Fasting serum TC ≥207 mg/dL (5.3 mmol/L), and mean serum TG concentration between 178 and 1335 mg/dL (2-15 mmol/L). Exclusion criteria: Intake of lipid lowering medications, fish oil, antioxidants, or other medication known to affect lipid metabolism. Sample size: 41	Changes in fasting lipids from baseline	Treatment with simvastatin alone reduced serum TC, TG, apo B, apo E from baseline, and increased HDL-C, and apo A-I. Addition of Lovaza to simvastatin treatment resulted in further reductions in plasma TG (*P* = .007) and apo-E (*P* = .035) levels, whereas HDL-C levels were unaffected. Treatment with Lovaza and simvastatin significantly lowered $TFPI_{ag}$ from baseline compared with placebo. Combination therapy with Lovaza significantly increased the levels of fibrinogen, $FVII_a$, and PAI-I_a from baseline levels, whereas $FVII_{ag}$ and $TFPI_a$ were reduced from baseline; no significant changes were noted in the placebo group. Combination therapy significantly reduced postprandial hyperlipemia, as measured by TG levels (TG AUC), incremental TG levels (TG iAUC) and TGR, compared with placebo. Moderate increase in glucose and a significant rise in insulin levels from baseline were also noted after treatment with Lovaza.	**Safety:** No adverse events were reported in the publications. Conclusion: The study concluded that Lovaza has an additive effect in lowering TG and TC, and raised HDL-C when added to statins. Lovaza + simvastatin combination therapy was effective in reducing $TFPI_a$ and $TFIP_{ag}$ in the fasting state and inhibited the activation of $FVII_a$ during postprandial lipemia and thus provided a beneficial effect on the hemostatic risk profile in patients with combined hyperlipemia.

Nordoy A, Hansen JB, Brox J, Svensson B.[90] Effects of atorvastatin and omega-3 fatty acids on LDL-C subtractions and postprandial hyperlipemia in patients with combined hyperlipemia. *Nutr Metab Cardiovasc dis* 2001;11: 7-16.	10-week randomized, double-blind, placebo-controlled study.	Atorvastatin 10 mg/day (all patients) for 5 weeks Lovaza 2 g/day + Atorvastatin 10 mg/day vs Placebo + Atorvastatin 10 mg/day for 5 weeks	Inclusion criteria: Patients, aged between 28 and 61 years, with combined hyperlipidemia including those who had been on cholesterol-lowering diet and treated with statins alone or with omega-3 fatty acids supplement. Mean serum TC ≥207 mg/dL (5.3 mmol/L) and serum TG levels between 178 mg/dL (2.0 mmol/L) and 1335 mg/dL (15.0 mmol/L) were required for the intervention. Exclusion criteria: Cardiovascular, liver or renal diseases; diabetes mellitus; alcoholism or other disorders that affect lipid metabolism. Sample size: 42	Changes in serum lipid parameters.	Atorvastatin alone significantly decreased serum TC (-30%), TG (-25%), LDL-C (-35%), and apoB and apoE (-20%) from baseline levels, whereas HDL-C (8%) and apoA1 (8.5%) levels were increased. Addition of Lovaza resulted in further increase in HDL-C levels (7%) from baseline compared with the changes in the placebo group, *P* <. 05. Combination therapy resulted in a significant redistribution of LDL-C subfractions with a decrease in both LDL_2 and LDL_3 from baseline levels. Evaluation of postprandial hypertriglyceridemia indicated reductions in total TG AUCs and iAUCs in both treatment groups; however, TGR was significantly reduced only in the Lovaza group. No significant changes were noted in the activities of lipoprotein lipase (LPL) and hepatic triglyceride lipase (HL) in either treatment group.	**Safety** No side effects were reported in the publication. Conclusion: The study concluded that addition of a low dose of Lovaza may further improve the risk profile for coronary heart disease in patients with combined hyperlipemia treated with atorvastatin. The authors noted that this effect was related to reduction of postprandial hyperlipemia and redistribution of LDL-C subfractions.

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